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Fluorination

Diethyl Fluoronitromethylphosphonate: Synthesis and Application in Nucleophilic Fluoroalkyl Additions

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Abstract: Diethyl fluoronitromethylphosphonate (**3**), a previously unknown compound, was synthesized by electrophilic fluorination of diethyl nitromethylphosphonate with Selectfluor. Base-induced decomposition of **3** was studied by NMR spectroscopy, which identified diethyl fluorophosphate and fluoronitromethane as the main decomposition products. C–H acidities [pK_a values in dimethyl sulfoxide (DMSO)] of **3**, 1-fluoro-1-phenylsulfonylmethanephosphonate (**1**; McCarthy's reagent), tetraethyl fluoromethylenebisphosphonate (**2**), and some nonfluorinated phosphonates were computed, and a good correlation between calculated and experimental pK_a values was found. The calculated C–H acidities increased in the sequence **2** < **1** < **3**. Diethyl fluoronitromethylphosphonate (**3**) was applied in the Horner–Wadsworth–Emmons reaction with aldehydes and trifluoromethyl ketones to provide new 1-fluoro-1-nitroalkenes with good to high stereoselectivities. Alkylation of **3** was successful only with iodomethane, however, conjugate additions of **3** to Michael acceptors such as α,β-unsaturated carbonyl compounds, sulfones, and nitro compounds allowed access to variously modified diethyl 1-fluoro-1-nitrophosphonates.

Introduction

Organic phosphates are ubiquitous in nature and display various important functions in living organisms such as protein activation, metabolism, information storage and transfer, cell signaling, and others.[1] It has long been understood that phosphonates containing nonhydrolyzable C–P bonds, are efficient phosphate mimics.[2] Furthermore, the concept of closer phosphate mimicking by α-fluorinated phosphonates, introduced by Blackburn and co-workers,[3] opened the area of applying various α-fluorophosphonates in biomedical studies.[4] Indeed, α-fluorinated phosphonates are often employed as enzyme inhibitors and metabolic probes.[4,5]

A number of monofluorinated phosphonates, including fluoromethylphosphonate,[6] (cyanofluoromethyl)phosphonate,[7] 2-(diethoxyphosphoryl)-2-fluoroacetate,[8] 1-fluoro-1-phenylsulfonylmethanephosphonate (McCarthy's reagent; **1**),[9] and tetraethyl fluoromethylenebisphosphonate (**2**)[3d,10] were prepared and used as building blocks in the synthesis of a variety of fluorine-containing phosphonates, other fluorinated compounds, and medicinal targets (Figure 1).[4]

However, diethyl fluoronitromethylphosphonate (**3**) is unknown and could represent a valuable building block for the synthesis of novel 1-fluoro-1-nitroalkenes (by the Horner–Wadsworth–Emmons reaction with aldehydes or ketones) or 1-fluoro-1-nitrophosphonates (by alkylation reactions or conjugate additions). The nonfluorinated derivative of **3**, diethyl nitromethylphosphonate (**4**), was used, for example, in the synthesis of diethyl [nitro(diazo)methyl]phosphonate, which was further converted into cyclopropane α-nitro-α-phosphonates[11] in a nitro-Mannich reaction with imines generated in situ to give N-protected 2-amino-1-nitroalkanephosphonates,[12] or in 1,3-dipolar cycloaddition with alkenes and 1-alkynes to give 3-diethoxyphosphoryl-4,5-dihydroisoxazoles and 3-diethoxyphosphorylisoxazoles, respectively.[13] 1-Fluoro-1-nitroalkenes are not known, but their nonfluorinated aromatic derivatives (β-nitrostyrenes) have been reported to exhibit a variety of biological activities such as the ability to down-regulate the immune response in humans.[14] Moreover, β-nitrostyrenes are described as selective human telomerase inhibitors,[15] are cytotoxic for human cancer cell lines,[14] and represent a novel class of antibacterial agents.[16] The attachment of other substituents such as fluorine to the β-position of the β-nitrostyrene skeleton would be expected to lead to significant changes in chemical properties and bioactivities. In contrast to 1-fluoro-1-nitroal-

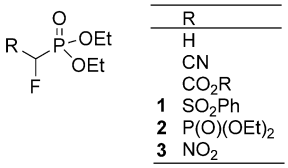

Figure 1. Examples of synthetically useful monofluoromethyl phosphonates.

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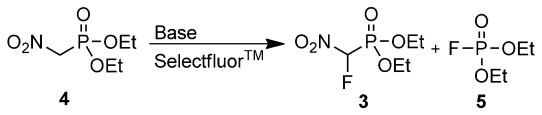
kenes, 1-fluoro-1-nitroalkanes are known and have been prepared by electrophilic fluorination of nitroalkanes.[17]

In this paper, we describe the synthesis of compound **3**, its stability and decomposition pathways in the presence of bases, calculate the pK_a of α-hydrogen dissociation, and show synthetic application of **3** in HWE reactions, alkylations, and conjugate additions. Our findings open new possibilities for the synthesis of selectively fluorinated compounds.

Results and Discussion

Diethyl fluoronitromethylphosphonate (**3**) was synthesized by electrophilic fluorination of diethyl nitromethylphosphonate (**4**) (Table 1).[17a] Phosphonate **4**, in the presence of sodium hydride or alkali metal hexamethyldisilazide and Selectfluor as an electrophilic fluorinating agent in mixtures of tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF), provided the desired product in low yields with the formation of significant amounts of toxic diethyl fluorophosphate (**5**). On the other hand, the use of an equimolar amount of potassium hydroxide in aqueous acetonitrile gave the product in good yield, free of any fluorophosphate (Table 1, entry 7). Employing *N*-fluorobenzenesulfonimide (NFSI) as fluorinating agent did not lead to improvements in the yield of **3**. By using the conditions shown in Table 1, entry 7 and replacing Selectfluor with NFSI gave only 7% yield of **3** (based on NMR spectroscopic analysis). Anhydrous conditions (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF) for NFSI fluorination of **4** provided only 16% **3** (based on NMR spectroscopic analysis).

Table 1. Optimization of diethyl nitromethylphosphonate fluorination.[a]



	Base (equiv)	Solvent (vol. ratio)	Selectfluor (equiv)	T [°C]	Yield of **3** [%][b]	Yield of **5** [%][b]
1	NaH (1.0)	THF/DMF (3:1)	1.0	0–25	32 (12)	27
2	NaH (1.1)	THF/DMF (3:1)	1.5	0–25	16	43
3	*n*BuLi (1.1)	THF/DMF (3:1)	1.1	−60 to 25	0	0
4	NaHMDS (1.1)	THF/DMF (3:1)	1.1	0–25	15	56
5	LiHMDS (1.1)	THF/DMF (3:1)	1.1	0–25	2	33
6	KOH (1.5)	MeCN/H_2O (1:1)	1.0	25	42 (20)	0
7	KOH (1.0)	MeCN/H_2O (2:1)	1.5	0	67 (48)	0
8	KOH (0.5)	MeCN/H_2O (2:1)	1.5	0	38 (25)	0
9	KOH (0.1)	MeCN/H_2O (2:1)	1.5	0	13	0

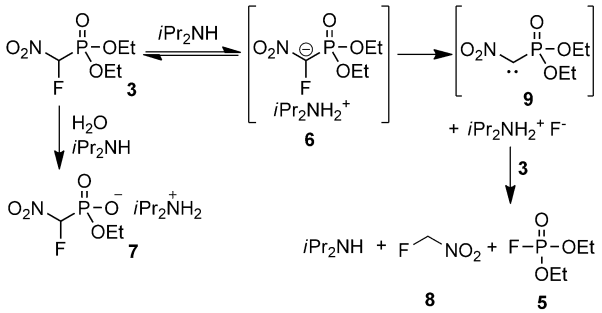
[a] Reactions were carried out using **4** (1 mmol, 1 equiv). [b] Conversions were estimated by GC/MS analysis; isolated yield given in brackets.

^{1}H NMR spectra revealed diastereotopic (nonequivalent) ethoxy groups on the phosphorus atom due to the presence of a chiral center on the α-carbon. An unusually low geminal coupling constant between the phosphorus atom and the CHF proton ($^2J_{P,H}$) of **3** was observed (Figure 2). The coupling constant was 0.3 Hz in [D_8]THF and no coupling could be observed with a 500 MHz NMR spectrometer in $CDCl_3$. However, in ^{1}H coupled ^{19}F and ^{13}C NMR spectra, coupling to both the phosphorus atom and to the CHF proton was clearly visible. In comparison, McCarthy's reagent (**1**)[18] and fluorobisphosphonate **2**[10b] have much larger values of $^2J_{P,H}$ (6.6 and 13.6 Hz, respectively). It is known[19] that geminal proton–phosphorus coupling constants of conformationally restricted phosphanes and phosphane oxides depend on the H-C-P-electron pair, and H-C-P=O dihedral angles and values close to 0 Hz were found at approximately 80° and 180° angles. Our systems have, however, low barriers for rotation around the P–C bond.

The formation of fluorophosphate **5** during the synthesis of **3** was at first surprising but became clear when the stability of **3** and its decomposition products were investigated. Phosphonate **3** has limited stability at ambient temperate and in the presence of bases; however, in pure form it can be stored under argon at 4 °C or below for several months without any significant decomposition. Addition of diisopropylamine to a solution of **3** in THF gave rise to salt **6** and partial hydrolysis to monoester **7** caused by the presence of residual water (Scheme 1).

Salt **6** slowly decomposes to diethyl fluorophosphate (**5**) and fluoronitromethane (**8**), possibly involving carbene **9**. However, the presence of **9** was not confirmed despite attempts to trap it as the corresponding cyclopropane derivative using styrene in the presence or absence of [$Rh_2(OAc)_4$] (in THF or DMF, −50 to 25 °C, 1–20 h).

The decomposition of **3** with diisopropylamine (1 equiv) was followed by ^{19}F NMR spectroscopic analysis (Figure 3) and the final products after one week of reaction time were diethyl fluorophosphate (**5**) and fluoronitromethane (**8**), each formed at about 40–50% NMR yield. The formation of **5** could be explained by decomposition of salt **6** to the fluoride ion, which reacts with **3** to give **5** and **8**. This is consistent with control experiments that showed that **3** and a solution of tetrabutylammonium fluoride (TBAF) in THF at 25 °C give **5** and **8**. The same products of decomposition of **3** were also observed with other bases such as Cs_2CO_3 or NaOEt in DMF; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-



Scheme 1. Proposed mechanism of decomposition of **3** with diisopropylamine.

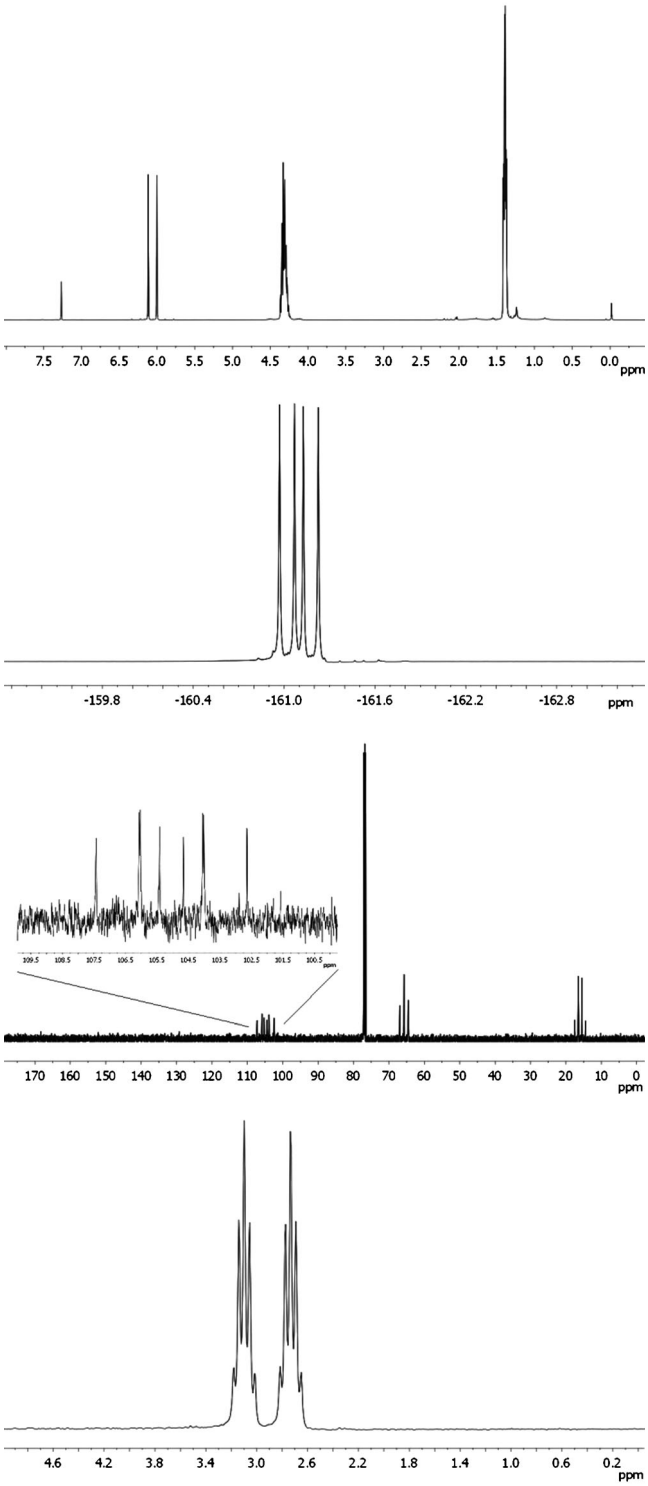


Figure 2. NMR spectra of **3** in $CDCl_3$: a) ^{1}H (500 MHz), b) ^{19}F (470 MHz), c) ^{13}C (126 MHz), d) ^{31}P (202 MHz).

diazabicyclo[2.2.2]octane (DABCO), or NaH in THF; and DBU in DMF. With iPr_2NEt in THF, no reaction took place.

For synthetic utilization of **3**, it was important to determine its pK_a value (corresponding dissociation of the proton at the α position) and compare it with pK_a values of related fluorinated and nonfluorinated phosphonates. Unfortunately, we were

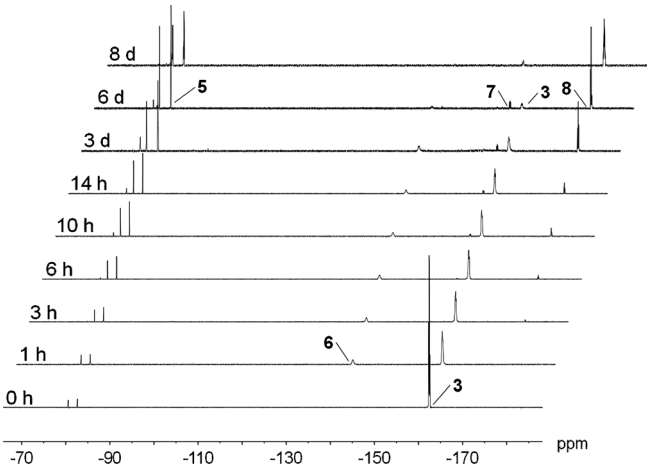
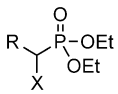


Figure 3. ^{19}F NMR spectra indicating the time-course of the reaction of **3** with diisopropylamine in THF at 25 °C.

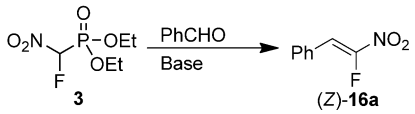
not able to determine the pK_a of **3** experimentally by electromigration methods due to its instability under basic conditions. Therefore, pK_a values were estimated by quantum chemistry calculations by using the RI-PBE + D3/def2-TZVP//RI-PBE + D3/def2-SVP 'model chemistry' together with the COSMO-RS solvation method (dimethyl sulfoxide).[20] The computed data were carefully benchmarked against available literature data[21] for phosphonates **10**–**13** (Table 2) and it can be seen that the difference between calculated and experimental values was, in most cases, between 1 and 2 pK_a units [more precisely, MAD(exp/theory) ≈ 1], which we consider to be excellent agreement for 'ab initio' predictions of acidity (pK_a) constants. These results gives us good confidence in the calculated values for the target systems (**1**–**4**, **14**, and **15**). As expected, fluorinated phosphonate **3** is more acidic than nonfluorinated **4** ($\Delta pK_a = 1.1$ in favor of the former) and acidity increased quite significantly in the sequence **2** < **1** < **3** and **14** < **15** < **4**. However, it is more difficult to explain the observed higher acidity of nonfluorinated **15** vs. fluorinated **1** (and also

Table 2. Experimental and computed pK_a values of selected diethyl phosphonates in DMSO.



Entry	Compound	R	X	pK_a, calcd (exp.)
1	**1**	$PhSO_2$	F	17.6
2	**2**	$P(O)(OEt)_2$	F	21.4
3	**3**	NO_2	F	8.1
4	**4**	NO_2	H	9.2
5	**10**	CN	H	15.2 (16.4)[21b]
6	**11**	CO_2Et	H	18.7 (18.6)[21b]
7	**12**	Ph	H	26.4 (27.6)[21a]
8	**13**	TMS	H	30.4 (28.8)[21a]
9	**14**	$P(O)(OEt)_2$	H	19.6
10	**15**	$PhSO_2$	H	15.7

Table 3. HWE reaction of **3** with benzaldehyde; optimization of reaction conditions.[a]



3 (*Z*)-**16a**

Entry	Base (equiv)	Solvent	*T* [°C]	*t* [h]	Yield of **16a** [%][b]	*Z*/*E*[c]
1	Cs_2CO_3 (1.0)	MeCN	25	1	0	–
2	NaH (1.1)	THF	−78 to 0	2	67	90:10
3	*t*BuOK (1.1)[d]	THF	−78 to 0	2	0	–
4	KOH (1.8)	MeCN[e]	0	0.5	6	–
5	iPr_2NH (1.0)	THF	−78 to 0	2	66	71:29
6[f]	NaH (1.5)	THF	−78 to 0	2	73	89:11
7[f]	iPr_2NH (1.5)	THF	−78 to 0	2	80	72:28
8[f]	DBU (1.5)	THF	−78 to 0	2	6	–

[a] Reactions were carried out using **3** (0.23 mmol, 1 equiv) and PhCHO (1 equiv) unless otherwise noted. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis of the isolated product. [d] With added 18-crown-6 (1.1). [e] Containing 1.5 vol.% water. [f] Excess **3** (1.5 equiv) was used.

14 vs. **2**) and we consider it a rather surprising finding. Apparently, the cumulative effect of three electron-withdrawing (deactivating) groups does not obey simple additive rules and quantum chemical calculations need to be used to obtain (at least semi)quantitatively correct results.

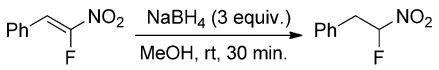
With compound **3** in hand, attention turned towards investigation of the Horner–Wadsworth–Emmons reaction with benzaldehyde as a model carbonyl compound to give (2-fluoro-2-nitrovinyl)benzene (**16a**). Several basic conditions were tested and the most competent bases were found to be sodium hydride (Table 3, entry 6) or diisopropylamine in THF (Table 3, entry 7). Other investigated bases led to the decomposition of **3** and the formation of **5** as the main product. Sodium hydride provided slightly higher *Z* stereoselectivities than diisopropylamine.

The optimized reaction conditions (Table 3, entries 6 and 7) were used in a scope and limitation study of the HWE reaction with various aldehydes and ketones (Table 4). Aliphatic aldehydes, including racemic citronellal, and aromatic aldehydes bearing both electron-acceptor and electron-donor groups provided 1-fluoro-1-nitroalkenes **16** in high yields and good *Z* stereoselectivities. In the case of 4-nitrobenzaldehyde, (*Z*)-**16f** formed almost exclusively. 3-(3,5-Dichlorophenoxy)benzaldehyde provided the fluorinated analogue of DPNS, a potent inhibitor of human telomerase.[15] Ketones were found to be largely unreactive, except for the highly electrophilic trifluoroacetophenone, which underwent the reaction in good yield and high stereoselectivity but only in the presence of sodium hydride.

Reduction of β-fluoro-β-nitrostyrene (**16a**) with sodium borohydride in methanol proceeded smoothly to give **17a**[17a] in good yield (Scheme 2). However, attempts to reduce the nitro group of **16e** with hydrogen in the presence of Raney nickel catalyst did not give the desired *gem*-1-fluoro-1-aminoalkene but, instead, led to the formation of (4-methoxyphenyl)acetonitrile (Scheme 3).

Alkylation of **3** with alkyl halide proved to be difficult (Table 5). High yields of alkylated products **18** were observed only with en excess of iodomethane and DBU as the base in THF (Table 5, entry 3). Other investigated bases (NaH, NaOEt, DABCO, Cs_2CO_3, Hünig's base in THF or DMF) were completely ineffective, whereas with diisopropylamine in THF only traces of **18a** were formed (Table 5, entry 4). Unfortunately, by using DBU as base, alkylating reagents other than iodomethane were either poorly reactive (1-iodobutane, allyl bromide) or unreactive (benzyl bromide or tosylate), and increasing the reaction temperature did not improve the yield because of concomitant decomposition of **3**.

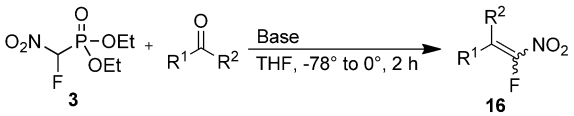
On the other hand, derivatization of **3** by conjugate addition to Michael acceptors has borne fruit. Several basic conditions for the desired transformation were tested and, once again, diisopropylamine in THF was identified as the best. The reaction of **3** with methyl vinyl ketone (**19a**) proceeded smoothly and the corresponding Michael adduct **20a** was obtained in almost quanti-



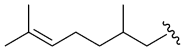
16a **17a**, 80%

Scheme 2. Reduction of β-fluoro-β-nitrostyrene (**16a**).

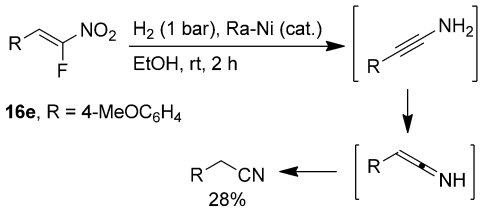
Table 4. HWE reaction of **3** with aldehydes and ketones.[a]



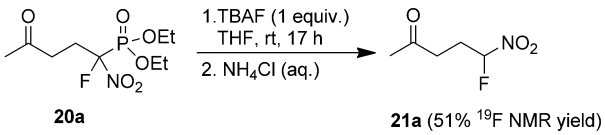
3 **16**

Entry	R^1	R^2	*Z*/*E*[b]	**16**	Yield[c] [%]	*Z*/*E*[d]
1	Ph	H	–	**a**	80	72:28
2	nC_6H_{13}	H	91:9	**b**	77	75:25
3		H	80:20	**c**	63	72:28
4	4-ClC_6H_4	H	78:22	**d**	81	65:35
5	4-$MeOC_6H_4$	H	67:33	**e**	71	73:27
6	4-$NO_2C_6H_4$	H	>98:2	**f**	73	>98:2
7	3-(3,5-dichlorophenoxy)phenyl	H	84:16	**g**	69	77:23
8	Ph	Me	–	**h**	0	–
9	Ph	Ph	–	**i**	0	–
10[e]	Ph	Me	–	**h**	0	–
11	Ph	CF_3	–	**j**	0	–
12[e]	Ph	CF_3	–	**j**	53	2:98

[a] Reactions were carried out using the carbonyl compound (0.23 mmol, 1 equiv), **3** (1.5 equiv), and iPr_2NH (1.5 equiv) in THF (1.5 mL) unless noted otherwise. [b] Determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. [c] Isolated yield. [d] Determined by ^{1}H NMR spectroscopic analysis of the isolated product. [e] Using NaH (1.5 equiv) as the base.



Scheme 3. Reduction of **16e** with hydrogen in the presence of catalytic Raney-nickel.

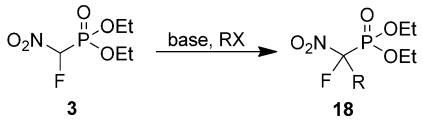


Scheme 4. Dephosphorylation of **20a** with TBAF.

tative yield (Table 6, entry 1). Even substochiometric amounts (0.3 equiv) of diisopropylamine or morpholine were sufficient for complete conversion into **20a**, but unfortunately these catalytic conditions could not be applied to other Michael acceptors. Phenyl vinyl ketone (**19b**) also reacted well with **3**; however, excess base and **3** were necessary to achieve a good yield. Phenyl vinyl sulfone, butyl acrylate, β-nitrostyrene (**19e**), and alkylidene-malononitrile **19f** provided the addition products **20e** and **20f** in good yields and low diastereoselectivities. In contrast, addition to 2-cyclohexenone (**19g**) did not give any addition product and the addition to diethyl vinylphosphonate (**19h**) provided product **20h** in the crude mixture; however, isolation by column chromatography gave only dephosphorylated **21h**. Similarly, dephosphorylated products **21c**, **21e**, and **21f** were observed in the crude reaction mixtures after conjugate addition of **3** to appropriate Michael acceptors. These compounds resulted from the reaction of **20** with fluoride anion derived from decomposition of excess **3**. Indeed, a control experiment revealed that **20a** undergoes dephosphorylation with TBAF in THF (Scheme 4). A similar dephosphorylation process was observed for ethyl 2-(dialkoxyphosphoryl)acetates and dialkyl (cyanomethyl)-phosphonates.[22]

A comparison of reactivities of carbanions derived from α-fluorophosphonates **1**–**3** reveals that the carbanion of **3** has relatively low nucleophilicity and steric bulk. This limits the scope of HWE reactions and alkylations compared with those of **1**[9] and **2**.[10] On the other hand, conjugate additions to both α- and β-substituted Michael acceptors are possible.

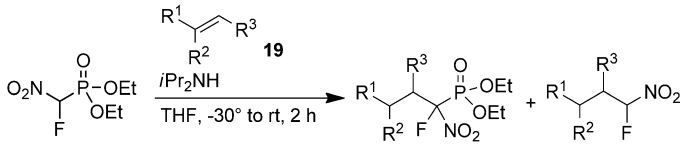
Table 5. Alkylation of **3** with alkyl halides.[a]



Entry	Base (equiv)	RX (equiv)	Solvent	*T* [°C]	*t* [h]	**18**	Yield [%][b]
1	DBU (1)	MeI (1.5)	THF	0–25	1	**a**	26 (22)
2	DBU (1)	MeI (1.5)	DMF	−30 to 25	2	**a**	0
3	DBU (1.2)	MeI (4)	THF	0–10	1	**a**	85 (72)
4	*i*Pr$_2$NH (1.1)	MeI (1.5)	THF	−78 to 0	1	**a**	5
5	DBU (1.2)	*n*BuI (4)	THF	0–25	2	**b**	15
6	DBU (1.2)	Allyl bromide (4)	THF	0–10	2	**c**	14

[a] Reaction conditions: **3** (0.33 mmol, 1 equiv), base, RX, THF or DMF (2 mL). [b] Based on ^{19}F NMR spectroscopic analysis using $PhCF_3$ as internal standard; isolated yield in brackets.

Table 6. Conjugate additions of **3** to Michael acceptors.[a]



Entry	**3** (equiv)	**19** (equiv)	R^1	R^2	R^3	*i*Pr$_2$NH (equiv)	**20**, Yield [%][b]	**21**, Yield [%][c]
1	1.0	**a** (1.5)	C(O)Me	H	H	1.0	**a**, 97	
2[d]	1.0	**a** (1.5)	C(O)Me	H	H	0.3	**a**, 88	
3	2.0	**b** (1.0)	C(O)Ph	H	H	2.0	**b**, 82	
4	1.0	**c** (1.0)	SO_2Ph	H	H	1.0	**c**, 48	**c**, 8
5	2.0	**d** (1.0)	CO_2*n*Bu	H	H	2.0	**d**, 66	
6	2.0	**e** (1.0)	NO_2	H	Ph	2.0	**e**, 67[e]	**e**, 11
7	2.0	**f** (1.0)	CO_2Et	CO_2Et	*n*Bu	2.0	**f**, 46[f]	**f**, 27
8	2.0	**g** (1.0)	H	-$(CH_2)_3$C(O)-		2.0	**g**, 0[c]	
9	2.0	**h** (1.0)	PO_3Et_2	H	H	2.0	**h**, 0[c]	**h**, 47[b]

[a] Reaction conditions: **3** (0.23–20.46 mmol, 1–2 equiv), *i*Pr$_2$NH (1–2 equiv), and **19** (1–1.5 equiv) in THF (1–2 mL). [b] Isolated yield. [c] Based on ^{19}F NMR spectroscopic analysis using $PhCF_3$ as internal standard. [d] MeCN was used as a solvent instead of THF. [e] *dr* = 51:49. [f] *dr* = 53:47.

Conclusion

A new fluorinated C1 reagent, diethyl fluoronitromethylphosphonate (**3**), was prepared and utilized in the stereoselective synthesis of new 1-fluoro-1-nitroalkenes by the Horner–Wadsworth–Emmons reaction with carbonyl compounds. Methylation with iodomethane and conjugate addition to Michael acceptors provided 1-fluoro-1-nitrophosphonates. Base-catalyzed decomposition of **3** was studied and fluoronitromethane and diethyl fluorophophate were identified as the main decomposition products. Based on quantum chemical calculations, the acidities of the α-hydrogen atoms increase in the series **2** < **1** < **3**. Thus, **3** is the strongest C–H acid of the three phosphonates, but the carbanion is the least nucleophilic. The title reagent proved to be highly useful in the synthesis of fluorinated organic molecules and promises to find many potential applications in life-science-related applications. Further exploration of the fluoroalkylation chemistry of **3** is underway in our laboratory.

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[1] M. W. Bowler, M. J. Cliff, J. P. Waltho, G. M. Blackburn, *New J. Chem.* **2010**, *34*, 784 – 794.

[2] a) R. Engel, *Chem. Rev.* **1977**, *77*, 349 – 367; b) C. Yuan, *Chin. J. Org. Chem.* **2001**, *21*, 862 – 868.

[3] a) G. M. Blackburn, *Chem. Ind. (London)* **1981**, 134 – 138; b) G. M. Blackburn, D. E. Kent, F. Kolkmann, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1119 – 1125; c) G. M. Blackburn, D. E. Kent, *J. Chem. Soc. Perkin Trans. 1* **1986**, 913 – 917; d) C. E. McKenna, P. D. Shen, *J. Org. Chem.* **1981**, *46*, 4573 – 4576.

[4] V. D. Romanenko, V. P. Kukhar, *Chem. Rev.* **2006**, *106*, 3868 – 3935.

[5] a) S. Halazy, A. Ehrhard, C. Danzin, *J. Am. Chem. Soc.* **1991**, *113*, 315 – 317; b) W. Chen, M. T. Flavin, R. Filler, Z.-Q. Xu, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3979 – 3988; c) C. J. Hamilton, S. M. Roberts, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1051 – 1056; d) Q. Wang, Z. Huang, C. Ramachandran, A. N. Dinaut, S. D. Taylor, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 345 – 350; e) C. C. Kotoris, W. Wen, A. Lough, S. D. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1271 – 1281; f) D. B. Berkowitz, M. Bose, T. J. Pfannenstiel, T. Doukov, *J. Org. Chem.* **2000**, *65*, 4498 – 4508.

[6] a) G. M. Blackburn, D. Brown, S. J. Martin, M. J. Parratt, *J. Chem. Soc. Perkin Trans. 1* **1987**, 181 – 186; b) R. Waschbüsch, J. Carran, P. Savignac, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1135 – 1140.

[7] a) E. Baader, W. Bartmann, G. Beck, P. Below, A. Bergmann, H. Jendralla, K. Kesseler, G. Wess, *Tetrahedron Lett.* **1989**, *30*, 5115 – 5118; b) Y. Wang, J. Lugtenburg, *Eur. J. Org. Chem.* **2004**, 5100 – 5110.

[8] See for example: a) H. Machleidt, R. Wessendorf, *Justus Liebigs Ann. Chem.* **1964**, *674*, 1; b) A. Thenappan, D. J. Burton, *Tetrahedron Lett.* **1989**, *30*, 5571 – 5574; c) A. Francesch, R. Alvarez, S. Lopez, A. R. deLera, *J. Org. Chem.* **1997**, *62*, 310 – 319; d) Y. Shen, J. Ni, *J. Org. Chem.* **1997**, *62*, 7260 – 7262; e) J. Kvicala, J. Plocar, R. Vlasakova, O. Paleta, A. Pelter, *Synlett* **1997**, 986 – 988; f) S. Sano, T. Ando, K. Yokoyama, Y. Nagao, *Synlett* **1998**, 777 – 779; g) K. Lee, Y. Choi, E. Gullen, S. Schlueter-Wirtz, R. F. Schinazi, Y. C. Cheng, C. K. Chu, *J. Med. Chem.* **1999**, *42*, 1320 – 1328; h) M. S. Marma, L. A. Khawli, V. Harutunian, B. A. Kashemirov, C. E. McKenna, *J. Fluorine Chem.* **2005**, *126*, 1467 – 1475.

[9] See for example: a) T. Koizumi, T. Hagi, Y. Horie, Y. Takeuchi, *Chem. Pharm. Bull.* **1987**, *35*, 3959 – 3962; b) J. R. McCarthy, E. W. Huber, T. Le, M. F. Laskovics, D. P. Matthews, *Tetrahedron* **1996**, *52*, 45 – 58; c) S. F. Wnuk, P. I. Garcia, Z. Wang, *Org. Lett.* **2004**, *6*, 2047 – 2050; d) D. B. Berkowitz, M. Bose, N. G. Asher, *Org. Lett.* **2001**, *3*, 2009 – 2012; e) S. Opekar, R. Pohl, V. Eigner, P. Beier, *J. Org. Chem.* **2013**, *78*, 4573 – 4579; See also ref.[5f]

[10] See for example: a) Y. Xu, L. Qian, G. D. Prestwich, *Org. Lett.* **2003**, *5*, 2267 – 2270; b) P. Cherkupally, A. Slazhnev, P. Beier, *Synlett* **2011**, 331 – 334; c) S. Opekar, P. Beier, *J. Fluorine Chem.* **2011**, *132*, 363 – 366; d) P. Beier, S. Opekar, M. Zibinsky, I. Bychinskaya, G. K. S. Prakash, *Org. Biomol. Chem.* **2011**, *9*, 4035 – 4038.

[11] A. V. Chemagin, N. V. Yashin, Y. K. Grishin, T. S. Kuznetsova, N. S. Zefirov, *Synthesis* **2010**, 259 – 266.

[12] R. Blaszczyk, A. Gajda, S. Zawadzki, E. Czubacka, T. Gajda, *Tetrahedron* **2010**, *66*, 9840 – 9848.

[13] Z. Rongyu, C. Jian, *Synthesis* **1990**, 817 – 819.

[14] K. C. Carter, Y. S. Finnon, N. N. Daeid, D. C. Robson, R. Waddell, *Immunopharmacol. Immunotoxicol.* **2002**, *24*, 187 – 197.

[15] J. H. Kim, J. H. Kim, G. E. Lee, J. E. Lee, I. K. Chung, *Mol. Pharmacol.* **2003**, *63*, 1117 – 1124.

[16] N. Milhazes, R. Calheiros, M. P. M. Marques, J. Garrido, M. N. D. S. Cordeiro, C. Rodrigues, S. Quinteira, C. Novais, L. Peixe, F. Borges, *Bioorg. Med. Chem.* **2006**, *14*, 4078 – 4088.

[17] a) W. Peng, J. M. Shreeve, *Tetrahedron Lett.* **2005**, *46*, 4905 – 4910; b) R. A. Kunetsky, A. D. Dilman, M. I. Struchkova, P. A. Belyakov, V. A. Tartakovsky, S. L. Ioffe, *Synthesis* **2006**, 2265 – 2270; c) H. Hu, Y. Huang, Y. J. Guo, *J. Fluorine Chem.* **2012**, *133*, 108 – 114; d) P. Butler, B. T. Golding, G. Laval, H. Loghmani-Khouzani, R. Ranjbar-Karimi, M. M. Sadeghi, *Tetrahedron* **2007**, *63*, 11160 – 11166; e) S. Rozen, A. Bar-Haim, E. Mishani, *J. Org. Chem.* **1994**, *59*, 6800 – 6803.

[18] Y. Shen, G. Wang, *Org. Lett.* **2002**, *4*, 2083 – 2085.

[19] W. G. Bentrude, W. N. Setzer in *Phosphorus-31 Nuclear Magnetic Resonance Spectroscopy in Stereochemical Analysis (Methods in Stereochemical Analysis)*, (Eds.: J. G. Verkade, L. D. Quin), Wiley-VCH, **1987**, pp. 380 – 382.

[20] A. Klamt, V. Jonas, T. Buerger, J. C. W. Lohrenz, *J. Phys. Chem. A* **1998**, *102*, 5074 – 5085.

[21] a) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456 – 463; b) C. Qi, Y. Du, Y. Lu, X. Sun, X.-M. Zhang, *J. Org. Chem.* **2009**, *74*, 8078 – 8085.

[22] a) A. Thenappan, D. J. Burton, *J. Org. Chem.* **1990**, *55*, 2311 – 2317; b) G. A. Artamkina, E. A. Tarasenko, N. V. Lukashev, I. P. Beletskaya, *Tetrahedron Lett.* **1998**, *39*, 901 – 904.

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