Stereoselective Synthesis of (*E*)-α-Fluorovinylphosphonates from α,α-Difluorophosphonates

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Abstract: α,α-Difluorophosphonates, which are readily available from alkyl halides and diethyl difluoromethylphosphonate, undergo elimination of hydrogen fluoride using alkali metal alkoxides to provide α-fluorovinylphosphonates in high yields and *E*/*Z* selectivities.

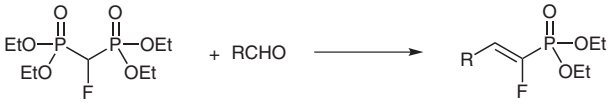
Key words: phosphonate, fluorine, elimination

Organic phosphate-containing compounds are ubiquitous in nature and take part in many important processes in living systems such as protein activation, metabolism, information storage and transfer, cell signaling and others. Phosphonates and their fluorinated derivatives, such as α,α-difluorophosphonates, α-fluorophosphonates, and α-fluorovinylphosphonates, have received considerable attention recently as nonhydrolyzable phosphate mimetics.[1,2] These compounds are important in the design of protein inhibitors and as probes for the elucidation of biochemical processes. α-Fluorovinylphosphonates have been used as precursors for α-fluorophosphonates (compounds that have been reported to be better phosphate mimics than either the methylene or difluoromethylene derivatives)[3] via hydrogenation reactions.[4] Additionally, some α-fluorovinylphosphonates display interesting biological activities.[5]

A number of methods for the preparation of α-fluorovinylphosphonates have been published. Fluoro-olefins undergo addition of phosphorus-containing nucleophiles, followed by fluoride elimination,[6] dehalogenation,[7] or dehydrohalogenation[8] to give fluorovinylphosphonates. Diels–Alder reaction, electrophilic iodination, or hydroamination of fluoroallenylphosphonates provide functionalized fluorovinylphosphonates.[9] Stereospecific palladium-based coupling protocols with α-bromo or α-iodo-α-fluoroolefins with dialkyl phosphites gives access to both (*E*)- and (*Z*)-fluorovinylphosphonates.[10] Zhang and Burton elegantly circumvented difficulties associated with the stereospecific preparation of isomerically pure α-halo-α-fluoro-olefins by kinetic separation (on phosphorylation) of *E*/*Z* mixtures to access both isomers of the α-fluorovinylphosphonates.[11] The Peterson olefination reaction of aldehydes, ketones, or trifluoroacetic esters with α-lithiated-α-fluoro-α-trimethylsilylmethylphosphonate generally gives *E*/*Z* mixtures of α-fluorovinylphosphonates.[12] Finally, the main synthetic route to α-fluorovinylphosphonates is the Horner–Wadsworth–Emmons (HWE) reaction of aldehydes or ketones with tetraalkyl fluoromethylene-bisphosphonate.[4,13] In this reaction, equimolar amounts of *n*-BuLi at –78 °C in ether solvent is typically used to generate the carbanion. HWE condensation with aldehydes (for examples, see Table 1, entries 1 and 3) or ketones (except sterically hindered ones) proceeds smoothly to give α-fluorovinylphosphonates in moderate to high yields and high (in case of aldehydes) to good (in case of ketones) *E* selectivities.

Modification of reaction conditions was carried out to improve the reaction. Employment of potassium carbonate instead of butyllithium gave no product, however, the use of a two-fold excess of cesium carbonate in *N*,*N*-dimethylformamide (DMF) at room temperature gave high yields of **1** (Table 1, entries 2 and 4). It was thus demonstrated that the cesium salt of fluoromethylene-bisphosphonate can be formed using mild base (Cs_2CO_3) and is stable in DMF at ambient temperature. However, the observed product selectivities were much lower. Reducing the temperature did not improve the outcome, and longer

Table 1 Formation of α-Fluorovinylphosphonates **1** by the HWE Reaction of Tetraethyl Fluoromethylene-bisphosphonate with Selected Aldehydes[a]



1

Entry	R	Method[b]	**1**, Yield (%)[c]	**1**, *E*/*Z*
1[13a]	Ph	A	92	93:7
2	Ph	B	98	63:37[d]
3[13a]	1-naphthyl	A	83	88:12
4	1-naphthyl	B	98	60:40[d]

[a] Reaction conditions: tetraethyl fluoromethylene-bisphosphonate (0.5 mmol), aldehyde (1 mmol, 2 equiv), solvent (2 mL), 3 h.
[b] Method A: *n*-BuLi (0.5 mmol, 1 equiv), Et_2O or THF, –78 °C to r.t.; Method B: Cs_2CO_3 (1 mmol, 2 equiv), r.t., DMF.
[c] Isolated yield.
[d] Determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture.

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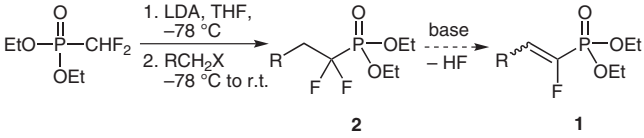
reaction times were needed for full conversion. Clearly, in the case of butyllithium as a base, chelation of the lithium ion with alkoxide and phosphonate oxygen atoms contributes significantly to the stereoselectivity of the elimination step.

Our previous work with α,α-difluoro-β-hydroxyphosphonates[14] and their base-induced phosphonate to phosphate rearrangement followed by HF elimination to (*Z*)-fluoroenol phosphates,[15] led us to the realization that fluorovinylphosphonates may result from HF elimination of α,α-difluorophosphonates **2** as outlined in Scheme 1.



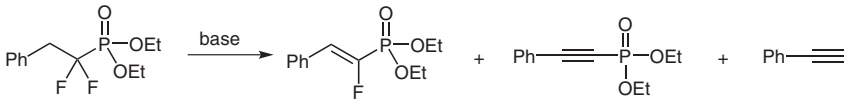
Scheme 1 Proposed synthesis of α-fluorovinylphosphonates **1** from α,α-difluorophosphonates **2** (X = Br, I, OSO_2CF_3)

α,α-Difluorophosphonates **2** are readily accessible by alkylation of difluromethylphosphonate anions with primary alkyl bromides, iodides or triflates in moderate to high yields. Zinc and cadmium reagents [$(EtO)_2P(O)MBr$, M = Zn, Cd] were also used for the synthesis of **2**.[1,16]

With compounds **2** in hand, investigations on hydrogen fluoride eliminations to α-fluorovinylphosphonates **1** were carried out. Phosphonate **2a** derived from benzyl bromide was used as starting compound and several bases were assessed to find appropriate reaction conditions (Table 2). With 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base at 60 °C, the reaction gave only low conversion into the desired product **1a** after 15 hours (Table 2, entry 1). LiHMDS in THF at low temperature provided a mixture of the desired α-fluoro-vinylphosphonate **1a** together with the product of a subsequent, second HF elimination – acetylenic phosphonate **3a** (Table 2, entry 2). With an excess of LiHMDS at ambient temperature, **3a** was detected as the only product (Table 2, entry 3). A two-fold excess of *t*-BuOK in DMF at –40 °C gave mainly phenylacetylene (**4a**) together with **3a**, while careful control of the amount of base and the reaction time resulted in good conversion into **1a** (Table 2, entries 4–6). With less basic potassium phenolate, the formation of side products was diminished, however, the reaction rate was unacceptably low. Good results were obtained using either sodium ethanolate or potassium trifluoroethanolate. Under optimized conditions (Table 2, entries 9 and 11), **1a** formed as the only product and was isolated in 98% yield. It is important to mention that, in all cases, HF elimination of **2a** gave exclusively the *E* isomer of **1a**.

The scope and limitations of the developed hydrogen fluoride elimination methodology were studied using the optimized reaction conditions (Table 2, entries 9 and 11). Starting from difluorophosphonate **2a**, both bases (EtONa or CF_3CH_2ONa) gave excellent results, however, for halogenated derivatives, the use of less basic CF_3CH_2ONa was preferred because, with sodium ethoxide, side reactions such as nucleophilic substitution of halogen atoms on the

Table 2 Optimization of Hydrogen Fluoride Elimination of **2a**[a]

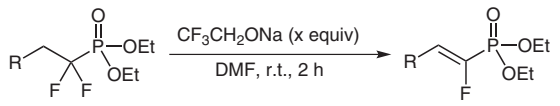


Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	**1a**, Conv. (%)[b]	**1a**, *E*/*Z*[c]	**3a**, Conv. (%)[b]	**4a**, Conv. (%)[b]
1	DBU (2.0)	THF	60	15	38	>99:1	0	0
2	LiHMDS (1.0)	THF	–30	0.5	7	>99:1	9	0
3	LiHMDS (2.5)	THF	r.t.	0.5	0	n/a	73	0
4	*t*-BuOK (2.0)	DMF	–40	2	0	n/a	29	71
5	*t*-BuOK (1.6)	DMF	–40	2	66 (47)	>99:1	8	25
6	*t*-BuOK (1.0)	DMF	–40	0.5	87	>99:1	4	5
7	PhOK (2.0)	DMF	r.t.	24	25	>99:1	0	0
8	EtONa (1.5)	DMF	r.t.	12	87	>99:1	0	10
9	EtONa (1.5)	DMF	0	1	>98 (98)	>99:1	0	0
10	CF_3CH_2ONa (2.5)	DMF	r.t.	2.5	93	>99:1	0	0
11	CF_3CH_2ONa (2.8)	DMF	r.t.	2	>98 (98)	>99:1	0	0

[a] Reaction conditions: **2a** (0.25 mmol), base, solvent (0.8 mL).
[b] Determined by GC/MS analysis, isolated yields in brackets.
[c] Determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. n/a – not applicable.

aromatic ring or fluorine substitution of the product took place. Therefore, sodium trifluoroethanolate was used for further investigations (Table 3). α,α-Difluoro-β-arylphosphonates **2a–f** underwent smooth HF elimination using sodium trifluoroethanolate in DMF. Isolated yields were excellent in all cases and only *E* isomers of the products α-fluorovinylphosphates **1a–f** were observed. With halogen-substituted phenyl groups (**2b–d**), only a small excess (1.1–2.0 equiv) of base was necessary for complete conversion. In other cases (**2a**, **2e**, and **2f**), a large excess of the base was required for full conversion and good yields of the products. α,α-Difluoro-β-alkenyl-phosphonates **2g** and **2h** also underwent smooth HF elimination, however, the observed product stereoselectivities were reduced. Increasing the amount of base improved the product *E*/*Z* ratio (Table 3, entries 8–10). On the other hand, α,α-difluoro-β-alkylphosphonate **2i**, under the reaction conditions, did not undergo HF elimination even using the much stronger base *t*-BuOK.

Table 3 Synthesis of α-Fluorovinylphosphonates **1**[a]



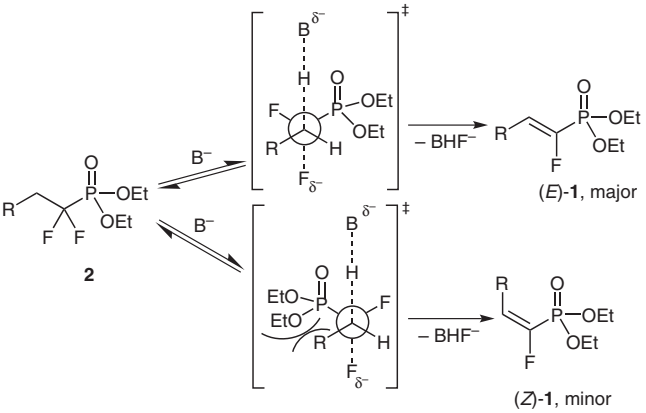
2 **1**

Entry	**2**	R	*x*	**1**	Yield (%)[b,d]	**1**, *E*/*Z*[c,d]
1	**2a**	Ph	2.8	**1a**	98	>99:1
2	**2b**	4-FC_6H_4	2.0	**1b**	99	>99:1
3	**2c**	3-ClC_6H_4	1.2	**1c**	98	>99:1
4	**2d**	2-BrC_6H_4	1.1	**1d**	98	>99:1
5	**2e**	4-MeC_6H_4	2.8	**1e**	91	>99:1
6	**2f**	4-$F_3CC_6H_4$	2.8	**1f**	93	>99:1
7	**2g**	CH_2=CH	3.0	**1g**	96	93:7
8	**2h**	(*E*)-PhCH=CH	1.1	**1h**	n.d.	81:19
9	**2h**	(*E*)-PhCH=CH	1.5	**1h**	92	84:16
10	**2h**	(*E*)-PhCH=CH	2.5	**1h**	89	90:10
11	**2i**	Bn	1.0	**1i**	0[e]	n/a

[a] Reaction conditions: **2** (0.45 mmol), CF_3CH_2ONa (*x* equiv), DMF (1.5 mL), r.t., 2 h.
[b] Isolated yield.
[c] Determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture.
[d] n.d. = not determined; n/a = not applicable.
[e] The same result was obtained using *t*-BuOK instead of CF_3CH_2ONa.

Clearly, the acidity of the hydrogen atoms vicinal to the fluorine atoms in **2i** is not high enough to perform the desired transformation.

The observed stereoselectivity can be explained by comparing the energies of the transition states leading to each isomer of **1** during the *anti* fluoride elimination as shown in Scheme 2. The transition state leading to (*E*)-**1** is lower in energy, because it does not suffer unfavorable steric interactions between the R group and the phosphonate group.



Scheme 2 Rationalization of the observed stereoselectivity in the formation of α-fluorovinylphosphonates **1**

In summary, an efficient and stereoselective one-step synthesis of (*E*)-α-fluorovinylphosphonates **1** from easily accessible α,α-difluoro-β-arylphosphonates or α,α-difluoro-β-alkenylphosphonates **2** is reported.[17]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **Synthesis of (*E*)-1a; Typical Procedure**. Trifluoroethanol (0.16 mL, 2.25 mmol, 5 equiv) was added to a mixture of sodium metal (29 mg, 1.26 mmol, 2.8 equiv) in anhydrous THF (2 mL). The mixture was stirred under argon until all sodium reacted. Solvent and excess alcohol were removed under reduced pressure and anhydrous DMF (1.5 mL) was added, followed by the addition of **2a** (125 mg, 0.45 mmol, 1 equiv). After stirring for 2 h at r.t., saturated aqueous NH_4Cl (10 mL) was added, the product was extracted into Et_2O (3 × 15 mL) and the combined organic phase was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and solvent was removed under reduced pressure. Purification of the crude product by silica gel flash chromatography (EtOAc–hexanes, 2:3), afforded pure (*E*)-**1a** (115 mg, 98%) as a colorless oil.[13a] R_f = 0.47 (EtOAc–hexanes, 2:3); IR (film): 3092, 3058, 3029, 2985, 2933, 2910, 1577, 1495, 1450, 1393, 1265, 1165, 1022, 757, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (dt, *J* = 7.1, 0.4 Hz, 6 H, 2 × CH_3), 4.16–4.27 (m, 4H, 2 × CH_2), 6.75 (dd, *J* = 42.3, 8.6 Hz, 1 H, CH), 7.33–7.43 (m, 3 H, $C_{Ar}H$), 7.61–7.63 (m, 2 H, $C_{Ar}H$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 6.2 Hz, CH_3), 63.2 (d, *J* = 5.4 Hz, CH_2), 123.1 (d, *J* = 29.9 Hz, CH), 128.7 ($C_{Ar}H$), 129.5 (d, *J* = 2.5 Hz, $C_{Ar}H$), 130.0 (d, *J* = 7.7 Hz, $C_{Ar}H$), 131.1–131.3 (m, C_{Ar}), 150.0 (dd, *J* = 286.1, 236.1 Hz, CF); ^{19}F NMR (376 MHz, $CDCl_3$): δ = –127.1 (dd, *J* = 97.8, 42.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 5.94 (d, *J* = 97.8 Hz); MS (EI): *m/z* (%) = 258 (95) $[M]^+$, 195 (17), 185 (70), 167 (18), 149 (89), 129 (64), 118 (61), 102 (100), 93 (30), 65 (45); HRMS (ESI^+): *m/z* $[M + H]^+$ calcd for $C_{12}H_{17}FO_3P$: 259.08939; found: 259.08926.