

Preparation and synthetic applications of α -fluorovinylphosphonium salts

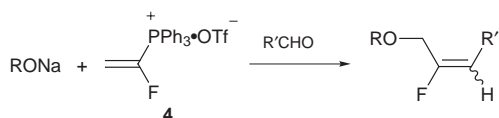
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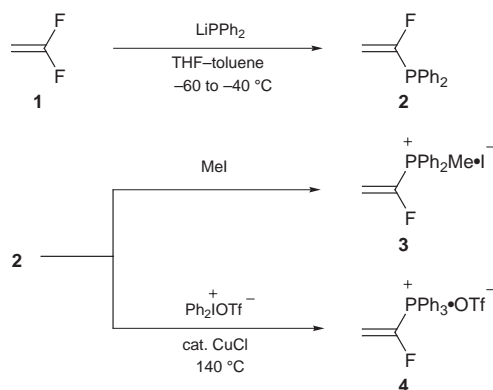
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α -Fluorovinylphosphonium salts **3** and **4** were synthesized and underwent Michael addition followed by Wittig olefination to give the corresponding monofluoroethylene compounds in good yields.

The replacement of a hydrogen atom by a fluorine atom often causes large changes in the biological activity of organic compounds, and the preparation of such fluorinated compounds has recently received much attention in the fields of medical and agricultural chemicals.¹ Although some methods for the direct exchange of the hydrogen by the fluorine are well-accepted, special techniques and equipment are required.² Thus, the development of versatile fluorinated building blocks has become a significant task in this field.³ We have considered the title compounds as promising candidates for a monofluorinated building block which would be stable and easy to handle. As vinyltriphenylphosphonium bromide (Schweizer reagent) exhibits excellent performance,⁴ we would expect similar reactivity for the title compound. This report describes the first preparation and reaction of the α -fluorovinylphosphonium salts as useful reagents for introducing a monofluoroethylene moiety into carbonyl compounds.⁵



Our synthetic route for the preparation of the α -fluorovinylphosphonium salts **3** or **4** is depicted in Scheme 1. Initially, we examined the convenient preparation of α -fluorovinylphosphine **2** as a precursor for the salts. Since it is well-documented that nucleophilic addition followed by elimination of the fluoride for producing 1,1-difluoroethylene derivatives is facile,⁶ it was therefore anticipated that the reaction of lithium diphenylphosphide⁷ and 1,1-difluoroethylene **1** should afford the facile preparation of the phosphine **2**. The modest yield we encountered when conducting the reaction in THF–toluene at -78 °C led us to controlling the reaction temperature. When the reaction was conducted over the temperature range of -60 to -40 °C, the yield improved to



Scheme 1

Table 1 Reaction of α -fluorovinylphosphonium salts with various aldehydes

Entry	R	R'	Yield (%) ^a	<i>E</i> : <i>Z</i> ^b
1 ^c	Me	Ph	43	52:48
2	Me	Ph	63	40:60
3 ^c	Et	Ph	52	53:47
4	Et	Ph	75	43:57
5	Et	4-MeOC ₆ H ₄	80	35:65
6	Et	4-PhC ₆ H ₄	70	47:53
7	Et	4-NCC ₆ H ₄	69	52:48
8	Et	2-naphthyl	77	41:59
9	Et	(<i>E</i>)-PhCH=CH	82	37:63
10	Et	PhCH ₂ CH ₂	trace	—

^a Isolated yield. ^b Determined by capillary GC–MS analysis. ^c Salt **3** was used in place of **4**.

86%. However, if the reaction temperature exceeded -40 °C, undesirable 1,1-bis(diphenylphosphinyl)ethylene was produced as a by-product.

Quaternization of the phosphine **2** with MeI proceeded smoothly to give the α -fluorovinylphosphonium iodide **3** in 91% yield; however, reaction of **2** with aryl halides or aryl triflates did not take place under various conditions. Kitamura and co-workers have described the direct *S*-arylation of benzo[*b*]thiophenes to produce the 1-arylbenzo[*b*]thiophenium salt.⁸ This prompted us to use the diaryliodonium salts for *P*-arylation of the phosphine **2** instead of *S*-arylation of the sulfides. After many unsuccessful experiments, the α -fluorovinyltriphenylphosphonium triflate **4** was finally obtained by the reaction of diphenyliodonium triflate in the presence of CuCl in 1,1,2,2-tetrachloroethane at 140 °C in 82% yield.[†] We believe that this *P*-arylation method provides a new route for the synthesis of the aryl phosphonium salts.

The β -ethoxy- α -fluoroethyltriphenylphosphonium ylide, generated *via* the addition of an ethoxide anion to **4** in ethanol at room temperature, reacted with benzaldehyde to provide 1-benzylidene-1-fluoro-2-ethoxyethane as a 43:57 mixture of the *E* and *Z* isomers in 75% yield (Table 1, entry 4).[‡] The *E*:*Z* ratio was determined by capillary GC–MS analysis. The geometrical isomers were characterized from their NMR spectra. The coupling constants with fluorine showed a value of 20 Hz for the *E* isomer and 39 Hz for the *Z* isomer. The effects of the reaction conditions on these relative *E*:*Z* ratios have not been studied. Some selected data are shown in Table 1. The reactivity of salt **4** was much higher than that of salt **3** (compare the yields in entries 1 vs. 2 and 3 vs. 4). Although aromatic aldehydes and an α,β -unsaturated aldehyde gave good results, the aliphatic aldehyde gave poor results. Studies on the synthesis of a variety of monofluorinated heterocyclic ring systems are now in progress in our laboratory.

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Notes and references

[†] Preparation of **2**: To a solution of lithium wire (0.54 g, 83.8 mmol) in 40 ml of THF was added diphenylchlorophosphine (6.0 ml, 33.4 mmol) at

room temperature under argon. The solution was stirred for 3 h and followed by the addition of 40 ml of toluene. After stirring for an additional 1 h, the solution was cooled to -60°C . At this temperature, argon was replaced with 1,1-difluoroethylene. The mixture was gradually warmed to -40°C and quenched with sat. NH_4Cl solution. After the usual workup, the residue was chromatographed on silica gel (hexane–EtOAc 100:1) to give the desired product (6.3 g, 86%): $\nu(\text{neat})/\text{cm}^{-1}$ 3056, 1622, 1482, 1435, 1153, 1095, 1027, 997, 916, 885, 742 and 694; $\delta_{\text{H}}(\text{CDCl}_3)$ 4.97 (1H, ddd, J 2.9, 6.3, 50.8), 5.39 (1H, ddd, J 2.9, 21.0, 23.4), 7.25–7.80 (m, 10 H); HRMS: 230.0661(M^+); Calc. for $\text{C}_{14}\text{H}_{12}\text{FP}$: C, 73.04; H, 5.25. Found: C, 72.96; H, 5.28%.

Preparation of **4**: A mixture of α -fluorovinylidiphenylphosphine **2** (1.47 g, 6.4 mmol), diphenyliodonium triflate (3.30 g, 7.7 mmol), copper(I) chloride (63.3 mg, 0.64 mmol), a catalytic amount of Cu wire (30 mg) and 4 Å molecular sieves (0.5 g) in 1,1,2,2-tetrachloroethane (1.5 ml) was heated at 140°C for 30 min under argon. After cooling the reaction mixture to room temperature, it was chromatographed on silica gel (CH_2Cl_2 then CH_2Cl_2 –acetone 2:1) to give the desired product (2.41 g, 82%). Further purification for the combustion analysis was conducted by recrystallization from Bu^tOH – Et_2O : mp 101.2 – 101.7°C ; $\nu(\text{KBr})/\text{cm}^{-1}$ 3137, 3062, 3007, 1632, 1588, 1581, 1486, 1482, 1441, 1370, 1257, 1227, 1172, 1152, 1114, 1029, 995, 935, 913, 760, 736, 709, 689 and 641; $\delta_{\text{H}}(\text{CDCl}_3)$ 5.79 (1H, ddd, J 6.4, 7.3, 49.3), 6.49 (1H, ddd, J 6.4, 21.5, 29.8), 7.7–8.0 (m, 15 H); m/z (FAB) 307 (M^+ – OTf); Calc. for $\text{C}_{21}\text{H}_{17}\text{F}_4\text{O}_3\text{PS}$: C, 55.27; H, 3.75. Found: C, 55.08; H, 3.67%.

‡ *General procedure*: To a solution of NaH (1.2 equiv.) in EtOH (5 ml) under Ar was added α -fluorovinyltriphenylphosphonium triflate (0.5 mmol) at room temperature. The resulting solution was stirred for 10 min, benzaldehyde (1.2 equiv.) was added to the solution, and the reaction mixture was stirred for 16 h. After the usual workup, column chromatography (silica gel, hexane–EtOAc 30:1) of the residue afforded 27.7 mg of (*E*)-1-benzylidene-2-ethoxy-1-fluoroethane and 39.1 mg of (*Z*)-1-benzylidene-2-ethoxy-1-fluoroethane (total 75% yield). (*E*)-isomer: $\nu(\text{neat})/\text{cm}^{-1}$ 2978, 2924, 2873, 1685, 1598, 1489, 1447, 1380, 1261, 1143, 1098, 997, 883, 750, 699 and 630; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.25 (3H, t, J 6.84), 3.58 (2H, q, J 6.83),

4.18 (2H, d, J 22.95), 6.45 (1H, d, J 20.02), 7.24–7.38 (5H, m); m/z 180 (30, M^+), 151 (46), 135 (60), 133 (56), 115 (80), 109 (100), 104 (30); Calc. for $\text{C}_{11}\text{H}_{13}\text{FO}$: C, 73.31; H, 7.27. Found: C, 73.54; H, 7.44%. (*Z*)-isomer: $\nu(\text{neat})/\text{cm}^{-1}$ 3025, 2978, 2865, 1695, 1598, 1496, 1450, 1351, 1099, 880, 755 and 694; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.27 (3H, t, J 6.83), 3.60 (2H, q, J 6.83), 4.12 (2H, d, J 15.14), 5.76 (1H, d, J 38.57), 7.21–7.53 (5H, m); m/z 180 (52, M^+), 151 (52), 135 (76), 133 (62), 115 (90), 109 (100); Calc. for $\text{C}_{11}\text{H}_{13}\text{FO}$: C, 73.31; H, 7.27. Found: C, 73.44; H, 7.35%.

- 1 J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; M. Schlosser, *Tetrahedron*, 1978, **34**, 3; *Biomedical Aspects of Fluorine Chemistry*, ed. R. Filler and Y. Kobayashi, Kodansha, Tokyo, 1982.
- 2 S. T. Purrington, B. S. Kagan and T. B. Patrick, *Chem. Rev.*, 1986, **86**, 997
- 3 J. R. McCarthy, E. W. Huber, T.-B. Le, F. M. Laskovics and D. P. Matthews, *Tetrahedron*, 1996, **52**, 45; T. Emet and G. Haufe, *Tetrahedron Lett.*, 1996, **37**, 7251; S. A. Fontana, C. R. Davis, Y.-B. He and D. J. Burton, *Tetrahedron*, 1996, **52**, 37; P. J. Crowley, J. M. Percy and K. Stansfield, *Tetrahedron Lett.*, 1996, **37**, 8233 and references cited therein.
- 4 E. E. Schweizer, L. D. Smucker and R. J. Votral, *J. Org. Chem.*, 1966, **31**, 467 and references cited therein.
- 5 The synthesis of α -fluorovinylphosphonates has been reported. G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1417; G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Chem. Commun.*, 1982, 1270.
- 6 H. F. Koch and A. J. Kielbania, Jr, *J. Am. Chem. Soc.*, 1970, **92**, 729.
- 7 E. J. Corey and M. A. Tius, *Tetrahedron Lett.*, 1980, **21**, 3535.
- 8 T. Kitamura, M. Yamane, B.-X. Zhang and Y. Fujiwara, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1215; T. Kitamura, M. Yamane, R. Furuki, H. Taniguchi and M. Shiro, *Chem. Lett.*, 1993, 1703.

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