The Novel Synthesis of Fluorinated Unsaturated Phosphonates

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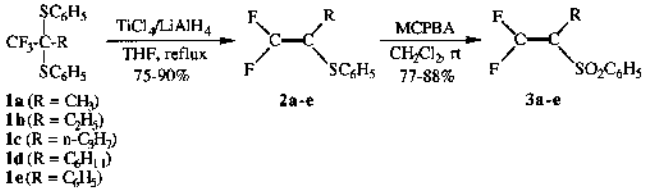
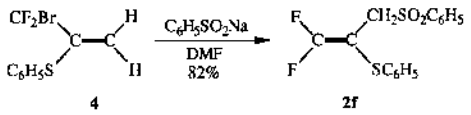
Received March 31, 1999

Phosphonic acids are very important compounds in biological system by virtue of their similarity to phosphates.[1] The replacement of oxygen in phosphate esters by a fluoromethylene (CHF) or difluoromethylene (CF_2) unit has been received much attention due to the enhancement of biological properties as compared to non-fluorinated analogs.[2-5] It has been well known that α-fluorinated phosphonates mimic phosphates in their isosteric and isopolar properties.[6,7] Theoretical calculations have proposed that monofluorophosphonate analogues show more similarity in isosteric and isopolar concept than difluorophosphonate ones.[8] Although a variety of biologically interesting compounds that contain the saturated α-monofluoroalkylphosphonate or α,α-difluoroalkylphosphonate-based mimics has been discovered in recent work *via* various methods,[9-13] the synthetic methods for the unsaturated α-monofluorophosphonates or α,α-difluorophosphonates have been quite limited.[14-17] Especially, the unsaturated α-monofluorophosphonates have been prepared by more limited methods.[18-20] A recent report has suggested that α-fluorovinylphosphonates are good precursors to α-monofluoroalkylphosphonates *via* reduction of double bond and also may have interesting biological properties.[19] The previous methods for the preparation of α-fluorovinylphosphonates include Wadsworth-Emmons reaction of lithium fluoromethylenebisphosphonate with aldehydes and ketones,[18] Peterson-olefination of lithium fluorotrimethylsilylphosphonate with aldehydes and ketones,[19] and reaction of lithium fluoromethylenediphosphonate with aldehydes.[20] However, β-phenylthio or β-phenylsulfonyl substituted α-fluorovinylphosphonates which can be transformed to another functionality *via* phenylthio or phenylsulfonyl group can not be prepared by previous methods. In this paper, we wish to describe a new synthetic method for the preparation of β-phenylthio or β-phenylsulfonyl substituted α-fluorovinylphosphonates via addition-elimination of corresponding β-phenylthio or β-phenylsulfonyl substituted α,α-difluoroolefins with triethylphosphite or sodium diethylphosphonate.

β-Phenylthio substituted α,α-difluoroolefins **2a-e** as starting materials can be prepared in 75-90% yields from the reaction of trifluoromethylated dithioketals **1a-e** with a mixture of $TiCl_4$ and $LiAlH_4$ in THF at reflux temperature for 3 h.[21] Further oxidation of **2a-e** with MCPBA in CH_2Cl_2 at room temperature for 3 h afforded the corresponding β-phenylsulfonyl substituted α,α-difluoroolefins **3a-c** in 77-88% yields. 1,1-Difluoro-3-phenylsulfonyl-2-phenylthio-1-propene (**2f**) as an another starting material was prepared in 82% yield from the reaction of 3-bromo-3,3-difluoro-2-phenylthio-1-propene (**4**) with sodium benzenesulfinate in DMF. The further oxidation of **2f** with MCPBA provided the corresponding disulfone in solution, but isolation of this disulfone compound was always failed probably due to the unstability of disulfone compound.





Triethylphosphite was used to carry out the addition-elimination reaction of **2a**, but the reaction did not proceed at all even under harsh reaction condition. However, the treatment of **2a** with sodium diethylphosphonate (1.5 equiv.) in THF at reflux temperature for 5 h resulted in the formation of *E* and *Z* isomeric mixture of β-phenylthio substituted α-fluorovinylphosphonate **5a** in 66% yield. *E* and *Z* isomeric ratio (*E* : *Z* = 35 : 65) can be determined by a magnitude of coupling constant between allylic protons and fluorine atom. It has been well known that a coupling constant between allylic protons and fluorine atom in the same side is bigger than that between allylic protons and fluorine atom in the opposite side.[22] Therefore, it was found that *cis* $J_{H,F}$ and *trans* $J_{H,F}$ in *Z* isomer are same (3.4 Hz) and trans $J_{H,F}$ and *cis* $J_{H,F}$ in *E* isomer are 2.3 Hz and 4.9 Hz respectively. Similarly, the reactions of **2b-e** with sodium diethylphosphonate (2-3 equiv.) under the same reaction condition provided adducts **5b-e** in 55-78% yields. In the formation of **5e**, *E* and *Z* isomeric ratio can not be determined by spectroscopic method. When **2f** was reacted with sodium diethylphosphonate under the same reaction condition, α-fluorovinylphosphonate **5f** was obtained in 42% yield. A major side product in this reaction was α,α-difluoroallylphosphonate 6[23] which was obtained in 8% yield. The use of nonpolar solvent such as toluene increased the formation of **6** up to 35% yield. However, low temperature (-78 °C) reaction condition afforded **5f** in 73% yield. A side product **6** was not detected in GC-MS spectroscopy at all in this condition. The results of these reactions are summarized in Table 1.

Triethylphosphite (3 equiv.) was successfully reacted with β-phenylsulfonyl substituted α,α-difluoroolefins **3a-c**. Therefore, the reaction of **3a** with triethylphosphite in

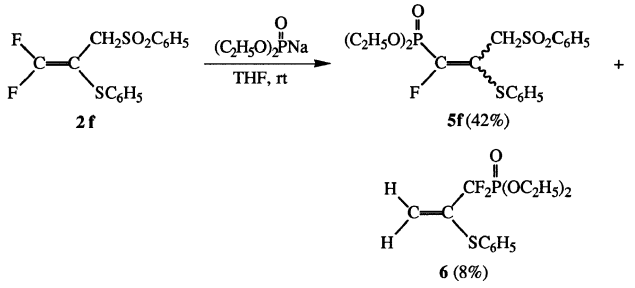
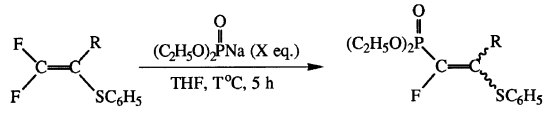


Table 1. The Preparation of β-Phenylthio Substituted α-Fluorovinylphosphonates **5**



Compound No.	R	X (equiv.)	T (°C)	*E*/*Z*	Yield (%)[a]
5a	CH_3	1.5	25	35/65	66
5b	C_2H_5	3.0	25	34/66	55
5c	*n*-C_3H_7	3.0	25	34/66	59
5d	C_6H_{11}	3.0	25	45/55	58
5e	C_6H_5	2.0	25	46/54[b]	78
5f	$CH_2SO_2C_6H_5$	1.5	-78	39/61	73

[a]Isolated yield. [b]E/Z isomer was not revealed.

CH_2Cl_2 at 25 °C for 72 h afforded an isomeric mixture of **7a** in 81% yield. The reaction under reflux condition to diminish the reaction time caused to decrease the isolated yield. *E* and *Z* isomeric ratio (*E* : *Z* = 10 : 90) can be determined by a magnitude of coupling constant between allylic protons and fluorine atom as in the case of compound **2a**. The use of sodium diethylphosphonate (1.5 equiv.) instead of triethylphosphite in this reaction provided a messy reaction mixture. The result did not much improve even under low temperature reaction condition. β-Phenylsulfonyl substituted α-fluorovinylphosphonates **7b-e** were prepared in a similar manner. The results of these reactions are summarized in Table 2. The reaction of **5d** with triethylphosphite was sluggish under the employed condition and thus provided **7d** in 39% yield. The oxidation of **5a-e** with MCPBA also provided β-phenylsulfonyl substituted α-fluorovinylphosphonates **7a-e** in 79-84% yields. The retention of stereochemistry was maintained in this oxidation reaction. However, the oxidation of **5f** with MCPBA resulted in the formation of a messy reaction mixture which could not be separated.

In a typical experiment for the formation of **5a**, sodium hydride (3.0 mmol) and diethylphosphite (0.41 g, 3.0 mmol)

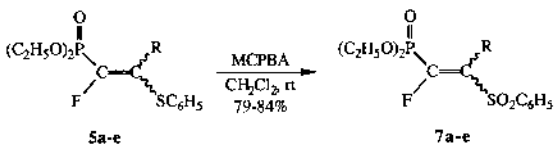
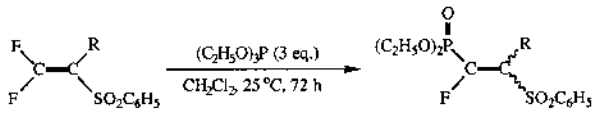


Table 2. The Preparation of β-Phenylsulfonyl Substituted α-Fluorovinylphosphonates **7**



Compound No.	R	Yield (%)[a]
7a	CH_3	81
7b	C_2H_5	75
7c	*n*-C_3H_7	76
7d	C_6H_{11}	39
7e	C_6H_5	72

[a]Isolated yield.

in dry THF (10 mL) were stirred at room temperature for 15 min under argon atmosphere. 1,1-Difluoro-2-phenylthiopropene (0.37 g, 2.0 mmol) was added at room temperature and then stirred for 5 h. The reaction mixture was quenched with saturated NaCl solution and extracted with ether (20 mL × 2). The ether solution was dried with anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with a mixture of *n*-hexane and ethyl acetate (2 : 1) provided **5a** in 66% yield. **5a**: colorless oil; ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.50-7.31 (m, 10H, *E* and *Z* isomer), 4.39-4.02 (m, 4H, *E* and *Z* isomer), 2.01 (t, *J* = 3.4, 3.4 Hz, 3H, *E* isomer), 1.93 (dd, *J* = 4.9, 2.3 Hz, 3H, *Z* isomer), 1.36 (t, *J* = 7.2 Hz, 6H, *E* and *Z* isomer); ^{19}F NMR (100 MHz, $CDCl_3$, internal standard $CFCl_3$) δ -107.51 (d, *J* = 102.0 Hz, 1F, *Z* isomer), -117.51 (d, *J* = 99.0 Hz, 1F, *E* isomer); MS, m/z (relative intensity) 304 (M^+, 65), 195 (100), 167 (52), 139 (87), 109 (19), 77 (9); IR (neat) 3073, 2984, 2930, 1616, 1583, 1477, 1441, 1263, 1169, 1022, 975, 751, 690 cm^{-1}.

In summary, β-phenylthio or β-phenylsulfonyl substituted α-fluorovinylphosphonates can be easily prepared in moderate to good yields via the addition-elimination reaction of β-phenylthio or β-phenylsulfonyl substituted α,α-difluoroolefins with phosphite nucleophiles. This novel method provided a simple, efficient and good yield preparation of β-phenylthio or β-phenylsulfonyl substituted α-fluorovinylphosphonates which can not be prepared *via* previous methods. β-Phenylthio or β-phenylsulfonyl substituted α-fluorovinylphosphonates are potential synthetic intermediates to provide useful biologically active compounds *via* transfomation of phenylthio, phenylsulfonyl group or double bond.

Acknowledgment. The authors wish to acknowledge the financial support of the Korea Research Foundation (1997-002-D00209) made in the program year of 1997.

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23. Spectroscopic data of **6** is as follows. **6**: oil; ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.51-7.30 (m, 5H), 5.96 (m, 1H), 5.26 (m, 1H), 4.31 (dq, J = 7.4, 7.2 Hz, 4H), 1.31 (t, J = 7.2 Hz, 6H); ^{19}F NMR (100 MHz, $CDCl_3$, internal standard $CFCl_3$) δ -105.62 (d, J = 111.4 Hz, 2F); MS, m/z (relative intensity) 322 (M^+, 87), 273 (12), 246 (18), 184 (100), 165 (67), 134 (14), 109 (61), 91 (30), 81 (39), 77 (31), 29 (15); IR (neat) 3058, 2984, 2908, 1709, 1496, 1456, 1274, 1022, 751, 691 cm^{-1}.