A Novel Sequential Transformations of Phosphonate. Highly Stereoselective Synthesis of Perfluoroalkylated α-Fluoro-α,*β* unsaturated Esters

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The phosphoryl-stabilized carbanion **2**, generated from diethyl (1-fluoro-1-carbethoxymethyl) phosphonate (**1**) and *n*-butyllithium in tetrahydrofuran (THF), was acylated by the addition of perfluoroalkanoic anhydride to give perfluoroacylated phosphonates (**3**). The latter were reacted in-situ with suitable organolithium derivatives. Elimination of phosphonic acid anion afforded perfluoroalkylated α-fluoro-α,*β*-unsaturated esters in 58−87% yields with the *E*-isomer produced exclusively or predominately. Thus the sequential transformations of phosphonate provides a convenient synthesis of the title compounds. The effect of base and solvent as well as reaction temperature has been investigated in more detail. A possible mechanism for the explanation of stereochemical results is proposed.

Introduction

Introduction of a fluorine atom or perfluoroalkyl group into compounds may increase the biological activity, and organofluorine compounds have been applied increasingly in pharmaceuticals, agrochemicals, and other field,[1] as examplified in vitamin A and pheromone chemistry.[2] α-Fluoro α,*β*-unsaturated esters have attracted much attention since they have been used successfully as intermediates in the synthesis of monofluorinated retinoids, insect sex pheromones, and pyrethroids.[3,4] In addition, biologically active compounds bearing a vinylic fluorine moiety have attracted much interest since it is in some enzyme inhibitors.[5] The earlier method for the preparation of α-fluoro-α,*β*-unsaturated esters involves the condensation of carbonyl compounds with toxic fluoroacetate or fluorooxaloacetate, but a mixture of product in poor yield was obtained.[6] The Horner−Wadsworth−Emmons (HWE) reaction was applied to the synthesis of these by use of dialkyl (fluorocarboalkoxymethyl)phosphonates.[7] An alternative approach is direct fluorination by use of spray-dried potassium fluoride.[8] Other methods using chlorofluorocarbene or organometallic reagents are also reported.[9] However most of methods reported are known to lack stereoselectivity. The method for the synthesis of perfluoroalkylated α-fluoro-α,*β*-unsaturated esters was very limited. Recently Thenappan and Burton reported that a reduction−olefination sequence was used to convert perfluoroalkyl carboxylic esters to perfluoroalkylated α-fluoro-α,*β*-unsaturated esters.[4]

Sequential transformations have attracted much interest in recent years because they provide a simple and efficient entry to complex compounds by including two or more transformation in a single operation to increase the complexity of substrate starting from commercially available, relatively simple precusors.[10] In our laboratory sequential transformations of phosphonium salts have been developed as a general synthetic approach for functionalized fluoroalkenes,[11] fluoroenynes,[12] fluorodienes[13] fluoro epoxides,[14] (fluoroalkyl)vinyl and (fluoroalkyl)epoxy phosphonates,[15] perfluoroalkylated allyl phosphonates[16] and sulfides,[17], perfluoroalkylated 1,4-alkadienes,[18] (perfluoroalkyl)vinyl dithianes,[19] and perfluoroalkylated heterocyclic compounds[20,21] which would be difficult to prepare otherwise. In our continuing investigation of the application of sequential transformations in organic synthesis, we report the sequential transformations of phosphonate and its application to the highly stereoselective synthesis of perfluoroalkylated α-fluoro-

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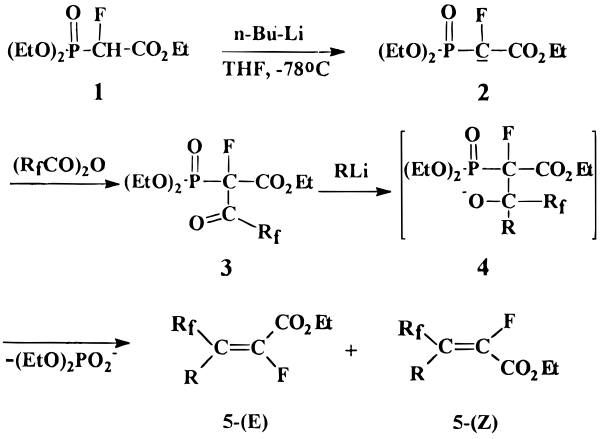
Scheme 1

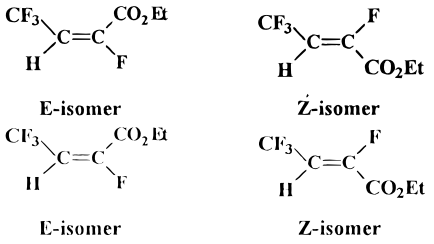


α,β-unsaturated esters. The methodology based on the sequential transformations of phosphonate is better compared to that of phosphonium salts because of the following advantages: (1) the starting material (phosphonate) is commercially available and cheap or easy to prepare, and (2) the simplicity of the isolation procedure demonstrates this methodology to be practical and it would have potential to be used in pharmaceutical and agrochemical industries.

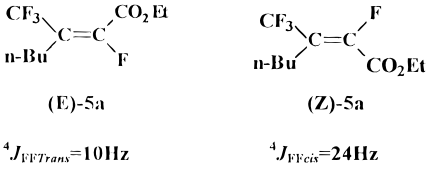
Results and Discussion

The reaction sequence is shown in Scheme 1. The phosphoryl-stabilized carbanion **2**, generated from the corresponding phosphonate and *n*-butyllithium in tetrahydrofuran (THF), was acylated by the addition of perfluoroalkanoic anhydride to give perfluoroacylated phosphonates **3** which, in the reaction medium, were attacked by organolithium reagents. Elimination of phosphonic acid anion afforded **5**. The key steps are the nucleophiles (RLi) attacking the perfluoroacylated phosphonates and elimination of phosphonic acid anion. The results are summarized in Table 1.

On the basis of data reported in the literature,[4] if the trifluoromethyl group is *trans* with respect to the F group (*E*-isomer), the $^4J_{FFtrans}$ is equal to 12 Hz, while for those



cis with respect to the F group (*Z*-isomer), the $^4J_{FFcis}$ is equal to 17 Hz. This compound was similar with compound **5a**, therefore, we assign **5a** with $^4J_{FF} = 10$ Hz



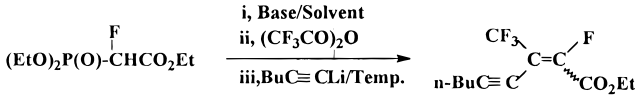
as the *E*-isomer and that with $^4J_{FF} = 24$ Hz as the *Z*-isomer. The same is true for the difluoro moiety

Table 1. Preparation of Perfluoroalkylated α-Fluoro-α,β-unsaturated Esters

compound	R	R_f	yield (%)[a]	*E*:*Z*[b]
5a	*n*-butyl	CF_3	58	80:20
5b	*n*-butylethynyl	CF_3	75	94:6
5c	phenylethynyl	CF_3	73	95:5
5d	2-thienyl	CF_3	80	0:100
5e	2-furyl	CF_3	65	100:0
5f	phenylethynyl	C_2F_5	71	100:0
5g	2-thienyl	C_2F_5	82	0:100
5h	2-furyl	C_2F_5	56	100:0
5i	phenylethynyl	n-C_3F_7	70	100:0
5j	2-thienyl	n-C_3F_7	87	12:88
5k	2-furyl	n-C_3F_7	61	100:0

[a] Isolated yields. [b] The ratios of *E*- to *Z*-isomers were estimated on the basis of NMR data.

Table 2. The Effect of Base, Temperature, and Solvent on the Stereochemistry and the Yield of 5b

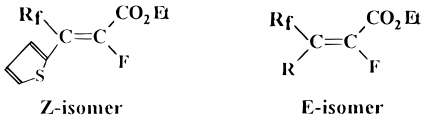


entry	base	solvent	temp (°C)	yield (%)[a]	*E*:*Z*[b]
1	*n*-BuLi	THF	−78	75	94:6
2	LDA	THF	−78	15	86:14
3	NaH	THF	−78	51	75:25
4	*n*-BuLi	THF	−30	64	82:18
5	*n*-BuLi	THF	0	56	84:16
6	*n*-BuLi	Et_2O	−78	68	91:9
7	*n*-BuLi	CH_2Cl_2	−78	60	81:19
8	*n*-BuLi	DMF	−78	0	

[a] Isolated yields. [b] The ratios of *E*- to *Z*-isomers were estimated on the basis of NMR data.

adjacent to the double bond in the pentafluoroethyl or heptafluoropropyl group.

Furthermore according to the sequence rules, in **5d**, **5g**, and **5j** (sulfur containing compounds), when the perfluoroalkyl group is trans with respect to the F group, the stereoisomer is assigned as the *Z*-isomer, while in other cases they are assigned as the *E*-isomer. For example,



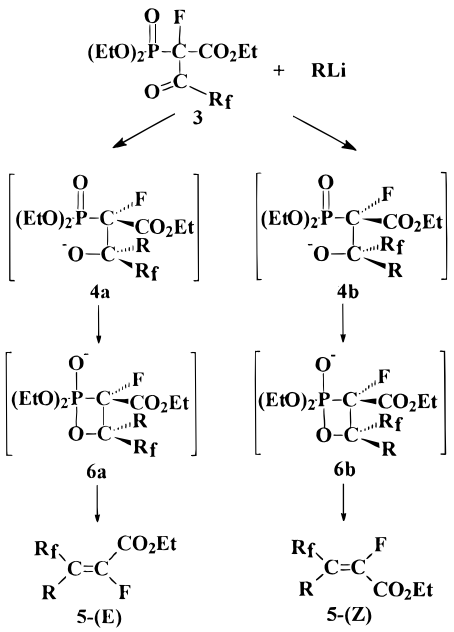
Hence the assignment is the reverse in sulfur-containing compounds as compared with other cases (see Table 1).

The effect of base and solvent as well as reaction temperature has been investigated in more detail with diethyl (1-carbethoxy-1-fluoromethyl)phosphonates (**1**) and lithium butylacetylide as reactants. The results are summarized in Table 2. The reaction proceeds best in THF and with *n*-BuLi as base; however, ether and methylene chloride are also acceptable. The reaction did not proceed in DMF because of incompatibility with the reagents. The yields of the reaction are decreased and a small change in the ratio of *E*- and *Z*-isomers is observed as the temperature is increased.

The stereochemical results may be rationalized as follows:

The mechanism for the formation of perfluoroalkylated α-fluoro-α,β-unsaturated esters is analogues to that of

Scheme 2



the intramolecular Horner−Wadsworth−Emmons reaction[22] and is outlined in Scheme 2.

The reaction is initiated by nucleophilic attack of nucleophile on the carbon−oxygen double bond of the carbonyl group, and for the additions containing an asymmetric α-carbon, the Felkin−Anh model of asymmetric induction[23] predicts the predominant diastereomer. The incoming nucleophile preferentially attacks the less hindered side of the plane containing the C=O bond. Therefore the relative steric bulk of F and CO_2Et play an important role in the stereoselectivity. The relative steric bulk of F is smaller than that of CO_2Et, the attack is from the rear (the side of plane containing small group) of **3** forming the intermediate **4a**; while the reverse is true for the attack from the front, forming intermediate **4b**. Each of those intermediates decomposes via a syn elimination, affording **5-(E)** or **5-(Z)**. In our case formation of **4a** will be favored over **4b** and the *E*-isomer was obtained exclusively or predominately (see Table 1).

In this one-pot reaction, three fragements unite together to give functionalized perfluoroalkylated alkenes where F and CO_2Et come from phosphonates, R comes from organometallic reagents, and R_f comes from perfluoroalkanoic anhydrides. This methodology is based on the fact that the strong electron-withdrawing effect of the perfluoroalkyl group makes the perfluoroalkyl ketone carbonyl more positive; therefore, the attack of nucleophiles at that position becomes easily. The characteristic feature of this methodology, in contrast with Wittig reactions, is the fact that nucleophiles are employed as attacking reagents which involve a variety of organometallic reagents, leading to the reaction of wide scope.

In conclusion, the sequential transformations of phosphonate have been applied to the synthesis of perfluoroalkylated α-fluoro-α,*β*-unsaturated esters, affording *E*-isomers exclusively or predominately. The effect of base, solvent, and reaction temperature has been investigated in more detail. A possible mechanism to explain the stereochemical results is proposed. The title compounds would potentially be employed as useful intermediates in the synthesis of fluorine-containing biologically active compounds.

Experimental Section

General. Analytical samples were purified by Kugelrohr distillation with the oven temperature (ot) given. ^{19}F NMR spectra are reported as ppm upfield from TFA. MS were obtained using ionization and are reported as *m/e* (relative intensity). All reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen. Solvents were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column.

Materials. All solvents were purified before use. THF was purified by distillation from sodium benzophenone ketyl. Diethyl (1-carbethoxy-1-fluoromethyl)phosphonates (**1**) were prepared according to the known procedure.[4a] Lithium acetylides were prepared by the reaction of *n*-butyllithium (3 mmol) and terminal acetylenes (3 mmol) in tetrahydrofuran (10 mL) for 15 min at 0 °C.

General Procedure for the Preparation of Perfluoroalkylated α-Fluoro-α,*β*-unsaturated Esters 5. *n*-Butyllithium (2 mmol in 1.5 mL of hexane) was added dropwise over 30 min to a stirred solution of diethyl (1-fluoro-1-carbethoxymethyl)phosphonate (2 mmol) in absolute THF (15 mL) at −78 °C under nitrogen. The mixture was stirred at −78 °C for further 0.5 h, and perfluoroalkanoic anhydride (2 mmol) was added to it in one portion. Stirring was continued at −78 °C for 1 h after which organolithium reagent (2 mmol) was added dropwise to the mixture which was stirred and allowed to warm to room temperature within 4 h. The reaction mixture was poured into water (30 mL) and the water layer was extracted with diethyl ether (3 × 15 mL). The combined organic layer was washed with brine (3 × 10 mL) and water (3 × 10 mL) and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was purified by column chromatography eluting with petroleum ether (60−90 °C)−ethyl acetate (99:1) to give the product **5**.

Ethyl 3-(Trifluoromethyl)-2-fluorohept-2-enoate (5a). Yield: 58%. bp: 50 °C/2 mmHg. E:Z = 80:20. IR (neat): 2960, 1750, 1670, 1300, 1080 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): δ 0.92 (t, 3H, J = 7.1 Hz), 1.20−1.54 (m, 7H), 2.26−2.44 (m, 0.80 × 2H), 2.56−2.66 (m, 0.20 × 2H), 4.22−4.38 (m, 2H) ppm. ^{19}F NMR ($CDCl_3$/TFA): δ −18.2 (d, 0.80 × 3F, J = 10 Hz), −15.8 (d, 0.20 × 3F, J = 24 Hz), 33.0−34.9 (m, 1F) ppm. MS: 243 ($M^+ + 1$, 60), 215 (33), 195 (32), 172 (36), 57 (45), 43 (100). HRMS calcd for $C_{10}H_{14}F_4O_2$ 242.0930, found 242.0878.

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Supporting Information Available: Characterization and analytical data of compounds **5b**−**k** and copies of proton NMR spectra to indicate purity of new compounds (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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