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Thia-Wittig-like Reactions as a New Route for the Stereoselective Synthesis of (*Z*)-Fluoroalkenoates

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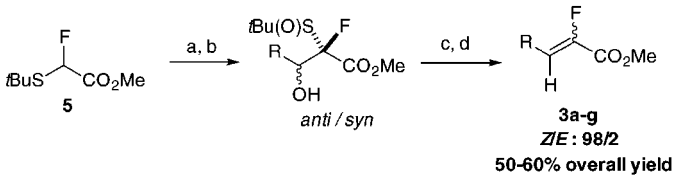
ABSTRACT



[a] (i) LDA; (ii) RCHO. [b] *m*CPBA, CH_2Cl_2. [c] SO_2Cl_2 , CH_2Cl_2. [d] - SO_2

Stereoselective syntheses of (*Z*)-fluoroalkenoates 3a–g have been developed in three steps from the readily available fluorosulfide 5 and aldehydes. This preparation, involving a Durst reaction, was highly stereoselective and led to fluoroalkenes in 50–60% overall yields, without purification of intermediates.

It is well-established that the replacement of hydrogen atoms of organic molecules by fluorine atoms strongly modifies their chemical, physical, and biological properties. Several applications reported the enhancement of the half-life of drugs due to the high stability of the carbon−fluorine bond or the synthesis of suicide inhibitors induced by the elimination of fluorine atom during the metabolization process.[1] Toward this goal, the fluorovinylic moiety has been introduced in various bioactive compounds such as sex pheromones, ribonucleotides, or retinal analogues.[2]

The widely used strategy to build (*E*)-fluoroalkenoates from aldehydes is the Horner−Wadsworth−Emmons reaction (HWE), involving the commercially available triethyl 2-fluoro-2-phosphonoacetate.[3] Alternative approaches based on concerted elimination of β-mesyloxy sulfoxides afforded (*E*)-fluoroalkenes with moderate selectivity.[4] Concerning the preparation of the *Z* isomer, the most elegant and direct approach consisted of alkylating the ethyl phenylsulfinyl fluoroacetate to produce exclusively (*Z*)-fluoropropenoates by a stereoselective elimination of sulfenic acid.[5] On the other hand, a phenylselenenyl fluoride equivalent has been used to produce (*Z*)-fluoroalkenoates from diazoesters.[6] Few methods have reported the selective synthesis of (*Z*)-fluoroalkenoates from aldehydes. The most efficient are the zinc−copper chloride promoted reaction of methyl difluoroacetate with carbonyl compounds,[7] the Peterson olefination involving aldehydes and α-fluoro-α-silyl acetate as a starting building block,[8] and the transformation of fluorinated sym-

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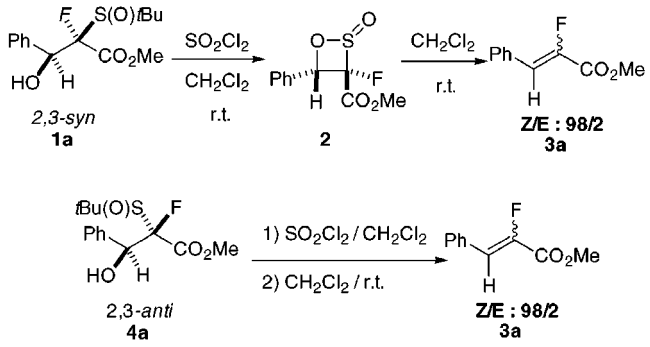
metrical diols by vanadium trichloride oxide.[9] Other routes have been reported using fluoromethyl phenyl sulfones or the isomerization of (*E*)-alkenoates.[10]

In this field, we were interested in new methodologies for the incorporation of the fluorovinylic moiety from aldehydes. We recently described a general synthesis of fluorinated β-hydroxysulfides, and we investigated their potentiality as alkene precursors.[11] Some methods described the conversion of β-hydroxysulfides to alkenes, leading to a mixture of stereoisomers.[12] Durst and others reported the selective synthesis of alkenes from β-hydroxysulfoxides. The formation of the intermediate cyclic sultine allowed the concerted elimination of the sulfinyl and hydroxyl functions to introduce a carbon−carbon double bond.[13] However, few synthetic applications of this reaction have been reported.

We carried out the oxidation of the pure *anti* and *syn* sulfides to sulfoxides **1a** and **4a**, using *m*CPBA at low temperature. Their oxidation led to a diastereoisomeric mixture of sulfoxides in quantitative yields, and products were used without purification to investigate the Durst reaction.

We treated the mixture of crude 2,3-*syn* sulfoxides **1a** with a solution of sulfuryl chloride (2 equiv) in dichloromethane. After 30 min of contact, the excess sulfuryl chloride was evaporated and then the crude products were stirred at room temperature in a dichloromethane solution. By monitoring the evolution of the reaction by fluorine NMR, we observed the apparition of two doublets (at −125.9 and −117.9 ppm) described as fluoroalkenes **3a**.[14] The ratio of the stereoisomers was stable from the beginning to the end of the transformation of the β-hydroxysulfoxides **1a**. After 30 h of stirring at room temperature and distillation of the crude product, finally we obtained a 98/2 mixture of alkenes **3a** isolated in 67% yield. The full characterization by 1D and $^1H\{^{19}F\}$ NOE difference NMR allowed us to assign the major product as the *Z* isomer **3a**. This selective formation of the (*Z*)-fluoroalkenoate **3a** could be explained if we considered the formation of the intermediate sultine **2** from the sulfoxide **1a**, as reported by Durst (Scheme 1).

Scheme 1

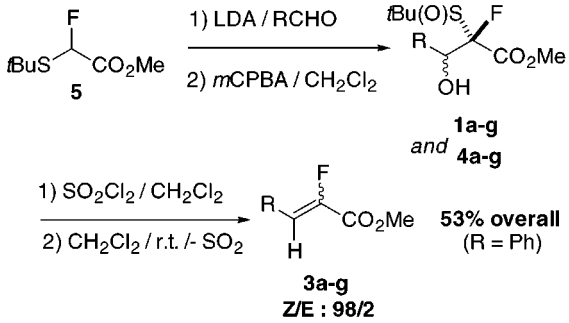


On the other hand, we carried out the same reaction from the 2,3-*anti* sulfoxides **4a**. Surprisingly the fluoroalkenoate **3a** was formed in a 98/2 *Z*/*E* ratio (Scheme 1). As previously observed by monitoring the reaction (^{19}F NMR), the ratio was stable during the process. The selective formation of the (*Z*)-alkenoate from the sulfoxides **4a** was unexpected, if we considered the mechanism involved from the sulfoxides **1a**. However, any isomerization of the pure (*E*)-alkenoate was observed in the same medium (SO_2Cl_2/CH_2Cl_2). The formation of the (*Z*)-**3a** from **4a** probably involves a radical or anionic elimination.

Theses results were generalized to develop a stereoselective synthesis of (*Z*)-fluoroalkenoates from the fluoroacetate **5** and aldehydes without purification of the diastereoisomers **1** and **4**.

The methyl *tert*-butylsulfanyl fluoroacetate (**5**) was treated with LDA at −78 °C to produce a mixture of *Z* and *E* enol ethers, which were trapped by aldehydes. After 2 h of stirring, a crude diasteroisomeric mixture of β-hydroxysulfides was obtained by acidic workup. After usual oxidation of the crude *m*CPBA, the mixture of sulfoxides **1a**−**g** and **4a**−**g** was then treated with sulfuryl chloride, leading selectively to (*Z*)-fluoroalkenoates **3a**−**g** (Scheme 2).

Scheme 2



By this three-step procedure from the fluorosulfide **5** and the benzaldehyde, the (*Z*)-fluoroalkenoate **3a** was formed stereoselectively and isolated in 53% overall yield (Table 1, entry 1).

This procedure was generalized to aromatic or aliphatic aldehydes (Table 1). The selectivity was still high, and fair overall yields from the three-step synthesis were obtained.

Table 1. Selective Synthesis of (*Z*)-α-Fluoro α,β-Unsaturated Esters

entry	R	product	overall yield (%)[a]	*Z*/*E* ratio[b]
1	Ph	**3a**[14]	53	99/1
2	*p*-(NO_2)Ph	**3b**	61	95/5
3	*n*-C_5H_{11}	**3c**[14]	47	88/12
4	*n*-C_8H_{17}	**3d**	60	94/6
5	*i*-Bu	**3e**	27[c]	97/3
6	*n*-C_3H_7	**3f**[7]	32[c]	94/6
7	*i*-Pr	**3g**[14]	34[c]	98/2

[a] Isolated overvall yield from **5**. [b] ^{19}F NMR of the crude. [c] Volatile products.

Due to their high volatility, fluoroalkenes **3e**−**g** were difficult to isolate. This method opens up a convenient route for the stereoselective synthesis of (*Z*)-fluoroalkenoates from readily available fluorinated building blocks **5**. The complete generalization of this method to ketones and highly functionalized aldehydes is under investigation to undertake the synthesis of modified biologically active compounds.

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Supporting Information Available: ^{1}H, ^{13}C, and ^{19}F NMR spectra and MS of **3b**,**d**−**e** and typical experimental procedure for their synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

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