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Claisen Rearrangement of Allylfluorovinyl Ethers

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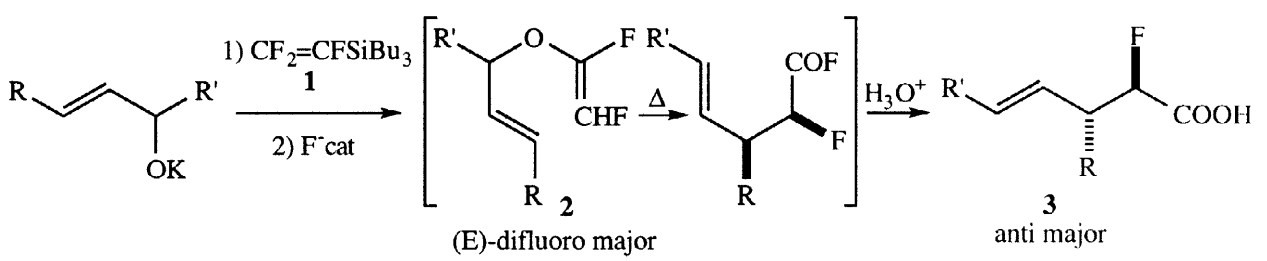
Abstract: One pot synthesis of α-fluoro β-substituted γ-unsaturated acids *via* a diastereoselective Claisen rearrangement of allylfluorovinyl ethers is described.

The Claisen rearrangement is considered as an useful synthetic transformation for the stereoselective construction of carbon-carbon bonds[1]. Two new asymmetric centers may be created diastereoselectively with concomitant regio- and stereospecific formation of a new double bond. The effect of a fluoro group on the reaction has already been described[2].

Herein, we report the Claisen rearrangement of allylfluorovinyl ethers **2** which offers the advantage of occuring at very low temperature (≈-30°C) leading with an internal asymmetric induction to 2-fluoro-4-alkenoic acids **3** (scheme1).



Scheme 1.

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The acids **3** are obtained by an one pot synthesis which includes four different steps: reaction between an allyl potassium alkoxide and trifluorovinylsilane **1**, protodesilylation with a fluoride source, selective Claisen rearrangement and hydrolysis of the acid fluoride.

Trifluorovinylsilanes **1** are readily prepared according to our method[3], starting from chlorotrifluoroethylene. The anion resulting from a chlorine-lithium exchange is quenched with the desired silylchloride.

$$CF_2{=}CFCl \xrightarrow[2)\ Bu_3SiCl]{1)\ n\text{-}BuLi} \underset{\mathbf{1}}{CF_2{=}CFSiBu_3} \qquad \text{Yield} \approx 80\%$$

We have chosen the tributylsilyl derivative because the hindrance of this silicon group limits the attack by the alkoxide. Moreover, its preparation is easy and its reactivity good at low temperature.

The first step involves a selective fluorine substitution by a metal alkoxide. D. Seyferth[4] already studied the reaction of sodium alkoxide (RONa, R = saturated alkyl) with trifluorovinylsilane. In THF, he reported that two products **4** and **5** were formed at room temperature.

$$CF_2{=}CFSiEt_3 \xrightarrow{RONa} \underset{\mathbf{4}}{ROCF{=}CFSiEt_3} + \underset{\mathbf{5}}{ROSiEt_3}$$

The alkoxide reacts according to an addition-elimination process to give the vinyl ether **4** with the fluorine atoms in a trans geometry. The yield of the latter is low because the alkoxide also reacts with the silicon leading to the formation of the silylated ether **5**.

Here, we show that the potassium alkoxide offers advantage of reacting in THF with the trifluorovinylsilane at very low temperature (-90°C) (temperature compatible with our later Claisen rearrangement which occurs at -30°C) giving product **4** in good yields. (This alkoxide does not react in Et_2O at -60°C, and with DMF as cosolvent, a complex mixture of products is obtained).

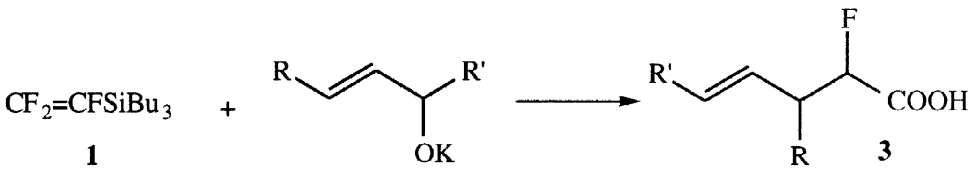
The protodesilylation reaction performed with a catalytic amount (10%) of Bu_4NF is very fast (15 min at -80°C/-60°C). A low temperature (-68°C) ^{19}F NMR study showed that, in the case of the crotylic alkoxide, the protodesilylation product has a stereoselectivity E/Z = 90/10[5].

By increasing the temperature of the reaction mixture to -30°C, the allylfluorovinyl ethers quickly undergo the Claisen rearrangement, giving after hydrolysis the fluoroacids **3**. We have already shown that the fluorine atom in α position to the oxygen atom was responsible for a substantial decrease of the rearrangement reaction temperature[2i]. This electronic effect has often been observed with other electronegative atoms such as oxygen (Ireland-Claisen) or nitrogen (Eschenmoser). With fluorine, the most electronegative element, this effect is further enhanced.

Finally, the hydrolysis of acid fluoride into acid is easy: in less than one hour at room temperature for the examples described here. Moreover, it is interesting to note that our method also allows to obtain an ester or an amide if an alcohol or an amine is added instead of water.

The results of this one pot synthesis are summarized in table 1.

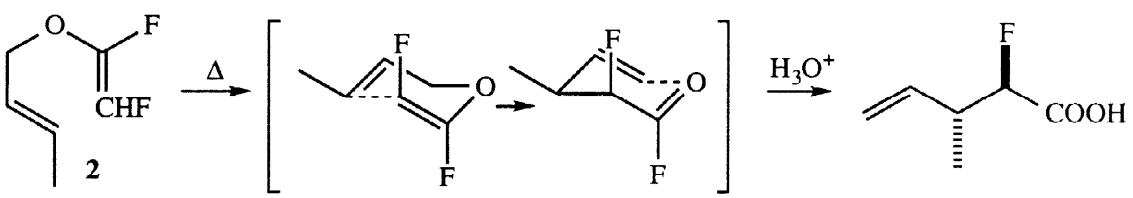
Table 1. Claisen rearrangement of allylfluorovinyl ethers.



	R	R'	Exp. cond[a] time (h)/T°C	Yield[b] (%)	dr[c] anti/syn	^{19}F NMR - δ(ppm)/CFCl$_3$ anti	syn
1	Me	H	2/-60	70	83/17[d]	-201.5	-200.5
2	n-Pr	"	"	57	82/18	-203.1	-198.1
3	i-Pr	"	3/-90	70	80/20	-204.5	-194.1
4	t-Bu	"	"	72	65/35	-201.5	-186.6
5	Ph	"	"	40	72/28	-199.2	-197.5
6	Me	Me	"	67	92/8	-201.7	-200.3
7	Me	Ph	"	28	60/40	-200.8	-200.6

a- two equivalents of potassium alkoxide in THF[6]; b- overall yields based on the starting vinylsilane **1**; yields for products isolated from the reaction mixture by an acid-base treatment (diluted H_2SO_4-$NaHCO_3$) followed by a subsequent purification with silica-gel chromatography (cyclohexane/AcOEt = 80/20 + 1% AcOH); c- dr: anti/syn diastereomer ratio determined by ^{1}H NMR; d- with commercial crotyl alcohol (E/Z = 94/6).

The Claisen rearrangement proceeds generally through a cyclic transition state with a favorable chair-like conformation. Thus trans difluorinated ether leads to the anti acid and the cis ether to the syn acid (scheme 2).



Scheme 2.

In table 1, we can note a variable amount of syn product. The latter must be mainly due to the presence of variable amount of cis difluorinated ether **2** and not to the transposition. In the following schemes, we try to explain the presence of the undesired cis isomer. The potassium trifluorovinyl anion must then abstract a proton from the solvent to give trifluoroethylene.

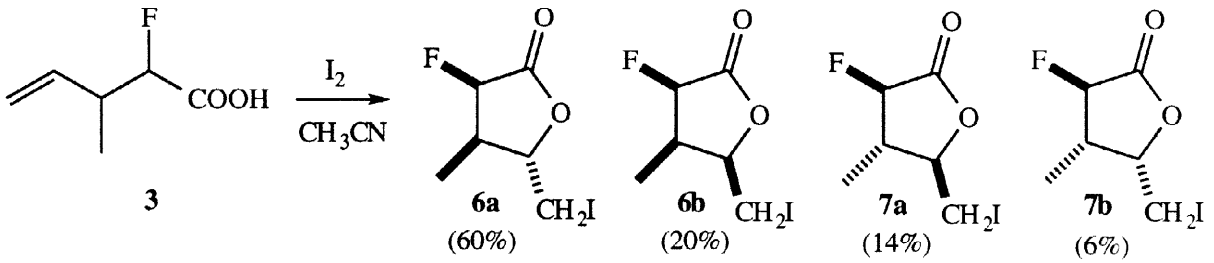
$$CF_2{=}CFSiBu_3 \xrightarrow{ROK} ROSiBu_3 + CF_2{=}CFK \xrightarrow{H^+} CF_2{=}CFH$$

We have also observed that the reaction below is very fast in THF at low temperature (-70°C) and leads to corresponding enol ether, as a mixture of E and Z isomers.

$$CF_2{=}CFH + ROK \longrightarrow ROCF{=}CFH \qquad E/Z \approx 3/1$$

In some cases (entry 4 and 7), we believe that the attack on the silicon must be more important in spite of our efforts.

In order to determine the configuration of the acid **3** (R = Me, R' = H), we have studied the ^{1}H (NOE), ^{19}F and ^{13}C NMR spectra of the lactones obtained from **3** after iodolactonization. When **3** (anti/syn ≈ 4/1) is treated with I_2 in CH_3CN, the iodolactonization yields a mixture of four iodolactones: **6** (as a mixture of **6a** and **6b**) and **7** (as a mixture of **7a** and **7b**) with **6/7** ≈ 4/1. As iodolactonization is a stereoselective process, the NMR studies allow to conclude that the major isomer of **3** is anti.



In conclusion, we have described the Claisen rearrangement of several allylfluorovinyl ethers. Good yields and variable diasteroselectivities have been obtained for the synthesis of 2-fluoro-4-alkenoic acids. The reaction diastereoselectivity results from the formation of **2** (E) predominantly and the intervention of a chair-like conformation in the transition state.

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References and notes

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5. ^{19}F NMR ($CH_3CH{=}CHCH_2OCF^2{=}CHF^1$): E isomer: -198.5 ppm (dd, F^1, $J(F^1/F^2)$ = 120 Hz, $J(F^1/H)$ = 74 Hz); -129.3 ppm (dd, F^2, $J(F^1/F^2)$ = 120 Hz, $J(F^2/H)$ = 3 Hz). Z isomer: -191.7 ppm (dd, F^1, $J(F^1/H)$ = 73 Hz, $J(F^1/F^2)$ = 9 Hz); -103.4 ppm (dd, F^2, $J(F^1/H)$ = 14 Hz, $J(F^1/F^2)$ = 9 Hz).
6. Typical procedure: allylic alcohol (10 mmol) is added to KH (10 mmol) in 40 ml of THF. After 1 h at +20°C, in this solution are successively added at -90°C, **1** (5 mmol) (stirring is continued for 3 h) and Bu_4NF (1M/THF) (0.5 mmol) (-80°C to -60°C/15 min). The mixture is hydrolyzed with H_2SO_4 (10%) at -50°C and the product is isolated after an acid-base treatment and a subsequent chromatography.