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An Improved Procedure for the Ireland-Claisen Rearrangement of Allyl Fluoroacetates

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Abstract: The Ireland-Claisen rearrangement of allyl fluoroacetates was effected by treatment of the starting esters with trialkylsilyltriflates in the presence of tertiary amines. The stereoselective formation of the products was rationalized as resulting from equilibration of the stereochemistry of the silyl ester products under the reaction conditions.

The Ireland-Claisen rearrangement is a powerful tool for acyclic stereocontrol and has found broad applications in organic synthesis.[1-3] The effect of fluorine on this rearrangement[4-7] and on [3,3] sigmatropic rearrangements in general[8-10] was investigated earlier. The same effective stereocontrol is possible in fluorinated systems as in hydrocarbon systems and has made this an important tool for preparative organofluorine chemistry.[11-14]

In our previous work however, the reactive silylketene acetal was formed by a rearrangement of a C-silylated material which was prepared by treatment of the lithium enolate of the appropriate fluoroacetate with chlorotrimethylsilane. While the stereoselectivity of the C,O-silyl migration was remarkable, synthetic application of the rearrangement was problematic. Under conditions which favored higher yields the presence of any excess base in the reaction mixture was sufficient to degrade the stereoselectivity of the process, presumably by epimerization of product α-fluorinated acids. Use of a closer to stoichiometric amount of base always resulted in significantly decreased yields. In order to use this rearrangement conveniently in synthesis we sought a new route to the preparation of the reactive silylketene acetal.

Treatment of the allyl fluoroacetates with a trialkylsilyl triflate in the presence of a tertiary amine at room temperature yielded the products of the Ireland-Claisen rearrangement in excellent yield and with very good stereoselectivity.[15] The (*Z*)-silylketene acetal apparently was formed selectively if the silyl ketene acetal stereochemistry is assumed to correlate directly with the product stereochemistry thru the chairlike transition state postulated for the rearrangement, ie., (*Z*)-silylketene acetal and (*E*)-ester olefin geometry as in 2 lead to rearrangement with *ul* topicity and *u* relative configuration of the product acid 3.[16]

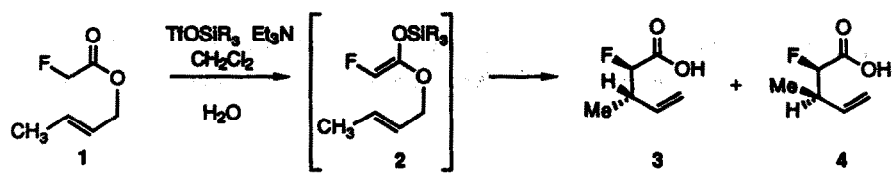
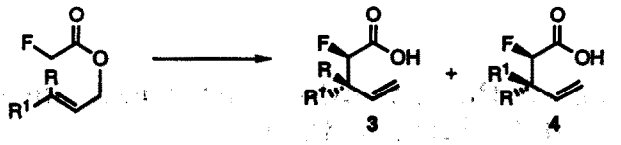


Table 1. Ireland-Claisen Rearrangement of Allyl Fluoroacetates.



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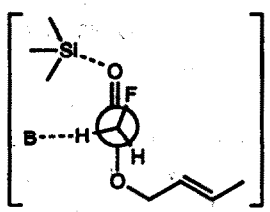
R	R^1	Trialkylsilyl Triflate	Reaction Conditions	Ratio 3 : 4[a]	Yield (%)[b]
H	Me	$Me_3SiOSO_2CF_3$	reflux[c]	3 : 1	>95
H	Me	$Me_3SiOSO_2CF_3$	room temperature[d]	5.8 : 1	85
H	Me	$Me_3SiOSO_2CF_3$	room temperature[e]	4.6 : 1	70
H	Me	$Et_3SiOSO_2CF_3$	reflux[c]	2.5 : 1	50
H	Me	$Et_3SiOSO_2CF_3$	room temperature	4 : 1	90
H	Me	*i*-$Pr_3SiOSO_2CF_3$	reflux[c]	6.3 : 1	83
H	Me	*i*-$Pr_3SiOSO_2CF_3$	room temperature	8 : 1	>95
H	Me	*t*-Bu$(Me)_2SiOSO_2CF_3$	room temperature	5.7 : 1	92
H	Me	*t*-Hexyl$(Me)_2SiOSO_2CF_3$	room temperature	6 : 1	40
Me	H	*i*-$Pr_3SiOSO_2CF_3$	room temperature	1 : 15	>95

a. Determined by ^{19}F NMR. b. Isolated products. c. Reactions were heated under reflux in dichloromethane solution for 15 h. d. Reactions were allowed to stir at room temperature for 72 h. e. Diisopropylethylamine was used.

Isolation of the intermediate silylketene acetal was not possible under the reaction conditions. The treatment of ethyl α-bromoacetate with triethylsilyl perchlorate in the presence of diisopropylethylamine at -40 °C had earlier been reported to exclusively form the (*Z*)-silylketene acetal.[17] However it also had been reported that triethylsilyl triflate was not successful in reactions to form silylketene acetals under these conditions.[17] It has been shown that while treatment of (*E*)-2-butenyl β,β,β-trifluoropropanoate yields products derived from [3,3]-sigmatropic rearrangement it does so with poor diastereoselectivity, presumably as a result of nonstereoselective enolization,[6] yet treatment of 2-butenyl tetrafluoropropionate under the same reaction conditions proceeds with excellent stereocontrol.[18] In the absence of a steric effect by fluorine, the stereochemical control in the formation of silylketene acetals derived from allyl fluoroacetates, may result from the influence of the stereoelectronic control of the acyclic transition state conformations likely involved in formation of the reactive silylketenes.[1] But, the influence of the steric demand of silylating reagent on the stereoselectivity of the reaction is then difficult to rationalize. The selectivity of the process improves in the order triisopropylsilyl > *tert*-butyl-dimethylsilyl> dimethyl-*tert*-hexylsilyl > trimethylsilyl ≈ triethylsilyl. Increasing steric demand favors increased stereoselectivity on formation of the product.

We propose that the stereoselectivity of the process results from differences in transition state energies along the reaction coordinate to form the reactive silylketene acetal, which on formation undergoes the rapid

[3,3]-sigmatropic rearrangement in the usual manner. With less bulky silylating reagents it is proposed that the transition state for formation of the silylketene acetal is earlier on the reaction coordinate and therefore more reactant like.[19] Since the energy difference between the synperiplanar conformer **5** and the anticlinal one **6** is only 200 cal/mol in ethyl fluoroacetate,[20] the stereoselectivity of silylketene acetal formation should be low.



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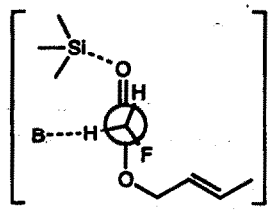

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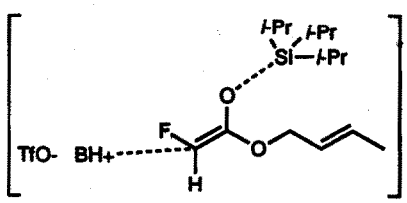
With the more bulky reagents and slower reaction, the Hammond postulate leads to the assumption of a transition state later on the reaction path. Since the transition state more closely resembles the product silylketene acetal, then the energy differences between the two possible transition states **7** and **8** may be greater.



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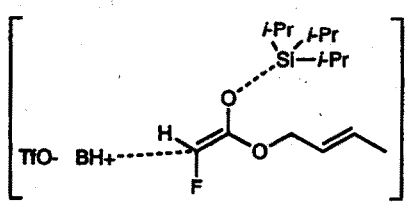

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The product 2-fluoro-3-methyl-pent-3-enoic acids are useful building blocks for the synthesis of fluorinated carbohydrates and nucleosides. Our preparation of these materials will be reported later.[16]

Acknowledgements. Financial support of this work by the National Science Foundation Grant number CHE-8901986, and DARPA Contract DAAL 0398KO198 is gratefully acknowledged.

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15. A typical procedure for the rearrangement of allyl fluoroacetates: *trans*-2-Butenyl fluoroacetate (6.45 g, 48.8 mmol) was added to a solution of 45 mL of dichloromethane and 33.6 mL of triethylamine (240 mmol) under an argon atmosphere. The mixture was cooled below -60 °C and triisopropylsilyl trifluoromethanesulfonate (21 mL, 78.1 mmol) was added to the mixture dropwise. The reaction mixture was allowed to warm to room temperature gradually and was stirred for 3 days. The reaction mixture was concentrated under reduced pressure. Ether (ca 100 mL) and a 1.3 M aqueous sodium hydroxide solution (150 mL) were added to the residue. The aqueous phase was separated and then was acidified with concentrated hydrochloric acid. Ethyl acetate was added to the solution and the organic phase separated, washed twice with water, dried over magnesium sulfate and concentrated in vacuo to yield 6.4 g (99%) of 2-fluoro-3-methyl-pent-4-enoic acid. ^{1}H NMR ($CDCl_3$): δ 5.83 (ddd, $J_{H3,H4}$ = 7 Hz, $J_{H4,H5,cis}$ = 10 Hz, $J_{H4,H5,trans}$ = 17 Hz, 1H, C<u>H</u>=CH_2), 5.17 (d, $J_{H4,H5,trans}$ = 17 Hz, 1H, CH=CH-<u>H</u>, trans), 5.13 (d, $J_{H4,H5,cis}$ = 10 Hz, 1H, CH=CH-<u>H</u>, cis), 4.87 (dd, $J_{H2,F}$ = 49 Hz, $J_{H2,H3}$ = 4 Hz, 1H, C<u>H</u>F), 2.79 (dddq, $J_{H2,H3}$ = 4 Hz, J_{H3,CH_3} = 7 Hz, $J_{H3,F}$ = 28 Hz, $J_{H3,H4}$ = 7 Hz, 1H, C<u>H</u>(CH_3)), 1.11 (d, J_{H3,CH_3} = 7 Hz, 3H, CH(C<u>H</u>$_3$)). ^{13}C NMR ($CDCl_3$): δ 174.48 (d, $J_{C1,F}$ = 25 Hz, C=O),137.29 (d, $J_{C4,F}$ = 3 Hz, <u>C</u>H=CH_2), 116.68 (CH=<u>C</u>H_2), 91.15 (d, $J_{C2,F}$ = 189 Hz, <u>C</u>HF), 40.14 (d, $J_{C3,F}$ = 19 Hz, <u>C</u>HCH$_3$), 13.44 (d, $J_{C,F}$ = 4 Hz, CH<u>C</u>H$_3$). ^{19}F NMR ($CDCl_3$): δ -200.51 (dd, $J_{H2,F}$ = 49 Hz, $J_{H3,F}$ = 28 Hz).
16. The relative stereochemistry of the product acids was confirmed by single crystal X-ray diffraction studies of carbohydrates prepared from them. (Araki, K.; Yun, W.Q.; O'Toole, J.; Toscano, P.J.; Welch, J.T. *Carbohydr. Res.* **1993**, submitted.) The relative stereochemistry is the opposite of that previously assigned by NMR methods.[4]
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