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A Novel Method for the Synthesis of α-Fluoroketones *via* Claisen Rearrangement

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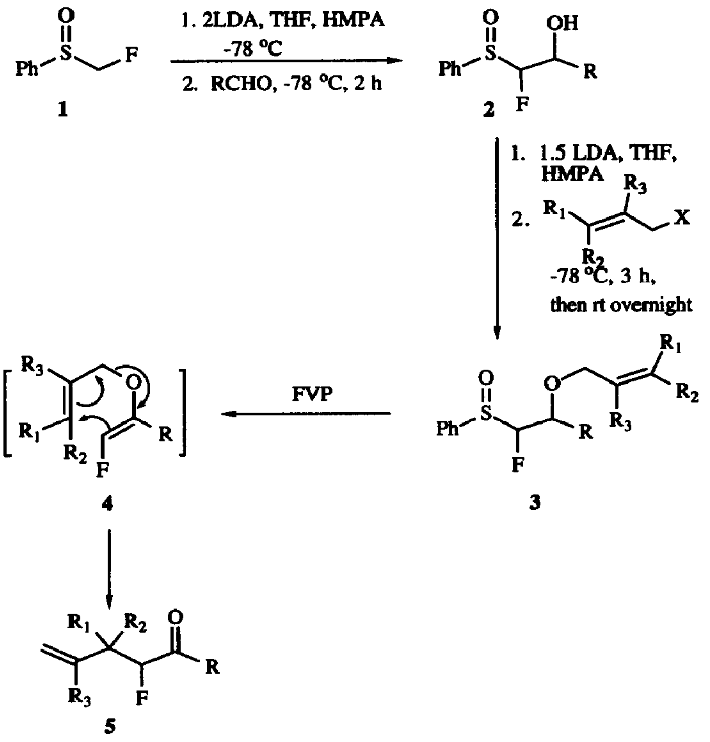
Abstract: Fluorine-facilitated Claisen rearrangement has been employed as a key step in the synthesis of α-fluoroketones 5. The elimination of sulfenic acid from the allyl ethers 3 are effected under FVP conditions.

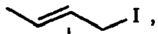
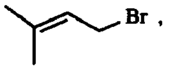
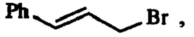
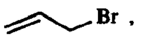
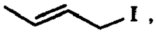
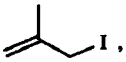
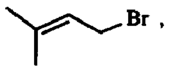
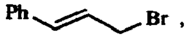
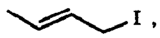
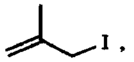
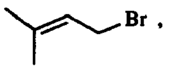
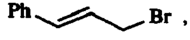
In the preceeding communication,[1] we have reported the synthesis of fluoromethylketones by flash vacuum pyrolysis (FVP) utilizing α-fluoromethyl phenyl sulfoxide **1** as a fluorinated one-carbon building block. The present letter deals with the novel synthesis of α-fluoroketones employing fluorine-facilitated Claisen rearrangement as the key step (**3** -> **5**).[2,3,4] The process is summarized in Scheme **1**.[5]



Scheme 1

The adducts **2** were prepared in high yields (R= C_8H_{17}, 82%; Ph, 83%; $PhCH_2$, 91%) using techniques reported earlier.[1] The allyl ethers **3** were prepared by the alkylation with the allyl bromides or iodides in good yields, using LDA as a base. The Claisen intermediate **4** was generated by FVP technique with the following conditions: reaction flask temperature, 216 °C and column temperature 305 °C at 0.1 mmHg. The results are summarized in Table **1**.

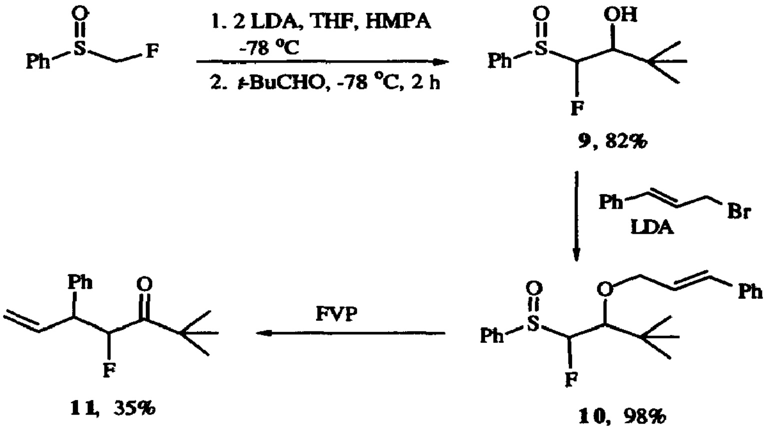
Table 1 Yields of Allyl Ethers **3** and α-Fluoroketones **5**.

	Allyl ethers 3, %		α–Fluoroketones 5, %[a]	
R = C_8H_{17}				
a)	 ,	98	83	
b)	 ,	75	93	
c)	 ,	83	97	
d)	 ,	72	28	+ $C_8H_{17}COCH_2F$ **6**, 71
e)	 ,	98	50	
R = Ph				
a)	 ,	75	83	
b)	 ,	64	82	
c)	 ,	51	84	+ $PhCOCH_2F$ **7**, 45
d)	 ,	63	54	
e)	 ,	66	98	
R = $PhCH_2$				
a)	 ,	76	85	
b)	 ,	64	94	
c)	 ,	84	98	
d)	 ,	79	32	+ $PhCH_2COCH_2F$ **8**, 55
e)	 ,	87	65	

[a] Products were isolated by PLC using hexane as an eluent.

The α-fluoroketones **5** are obtained in high yields except in the cases of **3d** (R= C_8H_{17}, Ph, $PhCH_2$; R_1=R_2= Me, R_3= H) in which the corresponding fluoromethylketones are also isolated. The formation of the fluoroketones **6**, **7** and **8** could be rationalized on the basis of the steric crowding of the transition state **4** causing it to fragments instead of forming a new carbon-carbon bond.

The reaction sequence in Scheme 1 has also been applied to a more sterically hindered aldehyde; pivalaldehyde. The fluoroketone **11** was isolated in moderate yield. The intermediates **9** and **10** were synthesized in high yields (Scheme 2).



Scheme 2

Our approach appears to be general for the synthesis of this type of fluoroketones. The outstanding features are the ease of the syntheses of intermediates **2** and **3** in high yields, and the final product fluoroketones can be readily purified by preparative thin-layer chromatography (PLC, silica gel).

References and Notes

1. Submitted for publication. Also see this communication for leading references on the chemistry and biology of fluorinated compounds.
2. For reviews on Claisen rearrangement see: a) Hill, R. K. in *Aymmetric Synthesis Volume 3*, Morrison, J. D., Ed. Academic Press, N. Y. **1984**, Chapter 8. b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. c) Blechert, S. *Synthesis* **1989**, 71.
3. An example of *in situ* generation of Claisen system (1,5-heterohexadiene) by the elimination of sulfenic acid has been reported: a) Mandai, T.; Ueda, M.; Hasegawa, S. I.: Kawada, M. and Tsuji, J. *Tetrahedron Lett.* **1990**, *31*, 4041. For related reactions see: b) Buechi, G. and Vogel, D. E. *J. Org. Chem.* **1983**, *48*, 5406. c) Paterson, I.; Huhne, A. N. and Wallace, D. J. *Tetrahedron Lett.* **1991**, *32*, 7601. d) Ireland, R. E.; Wipf, P.; Armstrong III, J. D. *J. Org.*

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4. A number of publications on fluorine-facilitated Claisen rearrangements has appeared. a) Normant, J. F.; Reboul, O.; Sauvetre, R.; Deshayes, H.; Masure, D. and Villieras, J. *Bull. Soc. Chim. Fr.* **1974,** 2072. b). Nakai, T.; Tanaka, K. Ogasawara, K. and Ishikawa, N. *Chem. Lett.* **1981,** 1289. c) Taguchi, T.; Morikawa, T.; Kitagawa, O.; Mishima, T. and Kobayashi, Y. *Chem. Pharm. Bull.* **1985,** *33,* 5137. d) Metcalf, B. M.; Jarvi, E. t. and Burkhart, J. P. *Tetrahedron Lett.* **1985,** *24,* 2861. e) Yuan, W.; Berman, R. J.; Gelb, M. H. *J. Am. Chem. Soc.* **1987,** *109,* 8071. f) Welch, J. T.; Plummer, J. S. and Chou, T. S. *J. Org. Chem.* **1991,** *56,* 353. g) Araki, K. and Welch, J. T. *Tetrahedron, Lett.* **1993,** *32,* 2251.

5. All new compounds were characterized by their spectral data and elemental analysis or HRMS molecular weight determination.

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