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# Claisen Rearrangement of α-(*F*-Alkyl)enol Ethers Prepared via Wittig Olefination of Allyl Perfluoroalkanoates

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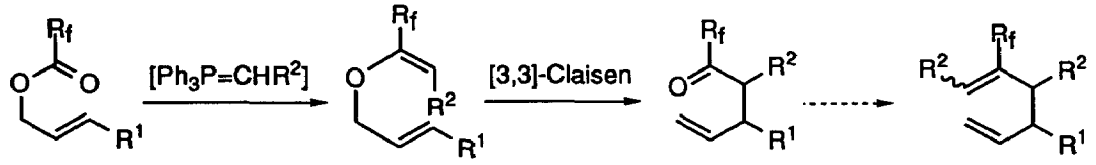
***Abstract:*** *The title rearrangement is shown to proceed at ca. 100 °C to afford the γ,δ-unsaturated perfluoroalkyl ketones. The stereochemistry of the Wittig and Claisen processes and the effect of the Rf-group in the Claisen process are discussed.*

Fluorine as a substituent can significantly affect the reactivity of molecular systems and hence often permits the reactions that cannot be underwent by the non-fluorinated counterparts.[1] Among such reactions is the Wittig olefination reaction of esters of perfluorinated carboxylic acids which affords the perfluoroalkyl ($R_f$)-substituted enol ethers.[2,3] An interest in the synthetic utility of the novel olefination process, coupled with our continuing interest in applications of the Claisen rearrangement in organofluorine synthesis,[4] prompted us to investigate the Claisen rearrangement of the $R_f$-substituted enol ethers **2** derived from allyl *F*-alkanoates **1** (Scheme 1).[5] This Claisen variant is of synthetic and mechanistic interest, since it might provide not only a new synthetic method for perfluoroalkyl ketones of current interest,[6] but also valuable information concerning the effect of $R_f$-substitution on the Claisen rearrangement in general.[4,7] Described herein are the realization of the Wittig- Claisen sequence and the interesting aspects thereof.

Scheme 1




**1** ($R^1$=$CH_3$) **2** **3** **4**

**a**, $R_f = CF_3$; **b**, $R_f = C_2F_5$

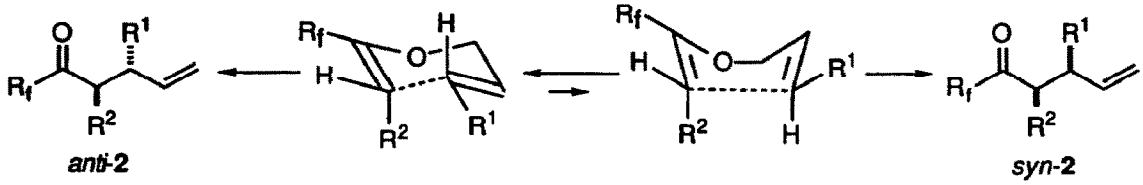
As a preliminary experiment, we first attempted the Wittig olefination of **1a** ($R_f$=$CF_3$, $R^1$=$CH_3$)[8] with 3 equiv. of the *n*-butylphosphonium bromide in refluxing benzene according to our "salt-free" procedure [$NaNH_2$ (3 equiv.), $(Me_3Si)_2NH$ (0.1 equiv.)].[2a] However, the major product thus obtained was neither **2a** nor **3a**, but a stereoisomeric mixture of the 1,5-diene **4a** ($R^2$=*n*-Pr) in 58% yield.[9] Likewise, the reaction of **1a** with benzylphosphonium bromide gave a stereosiomeric mixture of the corresponding 1,5-diene (**4a**,$R^2$=Ph) in 72% yield. Since the 1,5-dienes arise apparently from a further Wittig olefination of the Claisen product **3** once

formed, these findings suggest that the Claisen rearrangement concerned proceeds under the olefination conditions and much milder conditions are required for isolating the enol ethers.

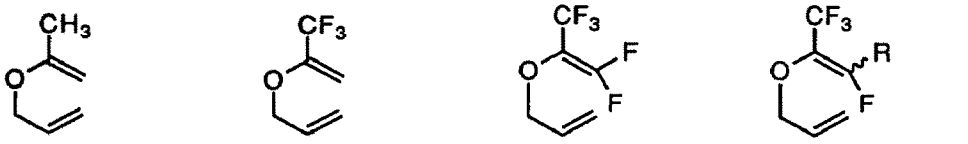
After several attempts,[10] we developed a procedure that allows us to isolate enol ether **2** without appreciable formations of **3** and **4**. Thus, the (*E*)-crotyl ester **1** was added at room temperature to an ylide solution, prepared in situ by treatment of 1.3 equiv of a phosphonium bromide with $NaNH_2$ (1.3 equiv) and

examples which employ the γ-phenylpropylphosponium bromide ($R^2$=$CH_2CH_2Ph$) as the ylide precursor.[11] Of particular interest and value is that, as previously reported,[2] the Wittig olefination is highly stereoselective to give the (*Z*)-enol ether almost exclusively.

Next, we examined the Claisen rearrangement of the (E)-crotyl (Z)-enol ethers thus isolated. Heating of **2a** and **2b** in toluene at 100 °C for 2 hr was found to afford the corresponding ketone **3** as an almost single diastereomer in quantitative yield (Table 1).[12] In view of the well-established relationship between the substrate geometries and the product stereochemistry in the Claisen rearrangement,[13] the major diastereomer might be assigned as anti as depicted below, although any attempt was not made to confirm the anti-configuration. Therefore, the Wittig-Claisen sequence can be achieved in a one-pot manner, while the yield of **3** was sightly lower due to some difficulties encountered in the isolation step.



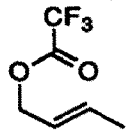
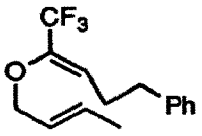
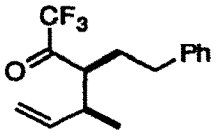
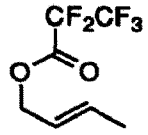
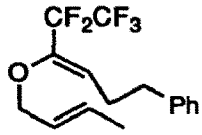
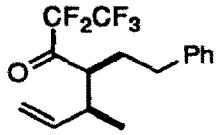

Furthermore, we made kinetic experiments of the present rearrangements to gain information about the Rf-substitution effect on the Claisen rearrangement in general. The rearrangements of **2a** and **2b** were found to follow the first order kinetic to provide the kinetic parameters as included in Table 1.[14] The preliminary data, compared with those reported for related variants, reveal significant trends in the present Claisen variant. The rearrangements of **2a** and **2b** are not much different in rate, but slightly faster than those reported the non-fluorinated parent one (**5**) and the $CF_3$-substituted parent one (**6**).[7] By contrast, the present rearrangements are seemingly more sluggish than those of the more fluorinated systems **7** and **8** which proceed smoothly around 40 °C and 60 °C, respectively.[4b] Considering that the introduction of an $R_f$ group would lower both the



**5** **6** **7** **8** (R = *n*-Bu)

HOMO and LUMO levels of the enol part,[15] the observed accelerating effect of the Rf-groups, albeit small in magnitude, are mechanistically interesting. More systematic studies are needed to understand the Rf-substitution effect on the Claisen rearrangement in general.

Table 1. The Wittig Olefination of Esters 1 and the Claisen Rearrangement of Enol Ethers 2.[a]

| Ester 1 | Enol ether 2[b] (%yield) | Ketone 3[b] (%yield) |
|---|---|---|
|  |  |  |
| **1a** | **2a** (65%) | **3a** (quant.) |
| | t 1/2 = 73.9 min (70 °C)<br>ΔH = 17.4 kcal/mol<br>ΔS = -5.5 cal/mol•K | |
|  |  |  |
| **1b** | **2b** (59%) | **3b** (quant.) |
| | t1/2 = 75.3 min (70 °C)<br>ΔH = 14.5 kcal/mol<br>ΔS = -1.02 cal/mol•K | |

[a] *The olefinations were run by the procedure described in the text and the rearrangements were carried out under reflux in toluene. Interestingly, the olefination of* ***1b*** *was much faster than that of* ***1a*** *(2 hr vs. 24 hr).* [b] *For* $^{1}H$ *and* $^{19}F$ *NMR data, see refs. 11 and 12.*

In summary, we have shown that the Wittig olefination of allyl perfluoroalkanoates followed by the Claisen rearrangement of the $R_f$-substituted enol ethers affords the γ,δ-unsaturated perfluoroalkyl ketones in high overall yields and stereoselectivities. Further extension of the present Wittig-Claisen sequence as well as further application of the Claisen rearrangement in organofluorine synthesis are in progress in our laboratories.

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**References and Notes**

1. Reviews: "Selective Fluorination in Organic and Bioorganic Chemistry" (ACS Symposium Series 456), Ed., Welch, J. T., American Chemical Society, Washington, D.C.,1991.
2. (a) Bégué, J.-P.; Bonnet-Delpon, D.; Mesureur, D.; Née, G.; Wu. S.-W. *J. Org. Chem.* **1992**, *57*, 3807. (b) Bégué, J.-P.; Mesureur, D. *J. Fluor. Chem.* **1988**, *39*, 271. (c) Bestmann, H. J.; Dornaauer, H.; Rostock, K. *Chem. Ber.* **1970**, *103*, 2011. (d) Bégué, J.-P.; Bonnet-Delpon, D.; Mesureur, D.; Ourévitch, M. *Mag. Res. Chem.* **1991**, *29*, 675.

3. A similar olefination of non-fluorinated esters requires the use of the Tebbe-type alkylidene titanium complexes:(a) Pine, S.H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.(b) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K.*J. Org. Chem.* **1987**, *52*, 4410.
4. (a) Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *25*, 3991. (b) Nakai, T.; Qian, C.-P.; Kobayashi, M.; Hirasa, T. *J. Fluor. Chem.* **1991**, *54*, 68.
5. Part of this work was presented at the 63rd Annual Meeting of the Chemical Society of Japan, Osaka, 1992. The Claisen rearrangement of the parent system ($R_f$=$CF_3$; $R^1$,$R^2$=H), prepared via the Tebbe reaction, has been reported (ref 7). After completion of this work, a paper has appeared on the Claisen rearrangement of similar systems ($R_f$=*n*-$C_4F_9$, *n*-$C_6F_{13}$, *n*-$C_8F_{17}$; $R^1$=H or an alkyl;$R^2$=H), prepared by an entirely different elimination reaction: Driss, C.; Chaabouni, M.M.; Baklouti, A. *Synth. Commun.* **1993**, *23*, 1887.
6. Review on the chemistry of perfluoroalkyl ketones: Bégué, J. -P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207.
7. Gajewski, J. J.; Gee, K. R.; Jurayj, *J. Org. Chem.* **1990**, *55*, 1813, and references cited therein.
8. Prepared in *ca.* 80% yield by reaction of (*E*)-crotyl alcohol with the *F*-carboxylic anhydride: $^{19}F$ NMR ($CDCl_3$,$CFCl_3$), -75 ppm (s) for **1a** ; -84 (t) and -122 ppm (q) for **1b**.
9. The $^{19}F$ and $^1H$ NMR spectral data of these 1,5-dienes are in accord with the assigned structures. The details will be described in a full paper.
10. For instance, when both the ylide generation and the olefination were carried out in THF at room temperature, the yield of **2a** was only 38% in the case of $R^2$=$CH_2CH_2Ph$ or a mixture of **2a**, **3a**, and **4a** resulted in the case of $R^2$=Ph.
11. The $^1H$ and $^{19}F$NMR spectra of **2a** and **2b** ($R^2$=$CH_2CH_2Ph$) showed a single set of peaks, suggesting that the enol ethers thus obtained are geometrically pure. **2a**:$^{19}F$ NMR ($CDCl_3$, $CFCl_3$), -70 ppm (s); $^1H$ NMR ($CDCl_3$, TMS), δ 1.70 (d, 3H), 2.4-2.8 (m, 4H), 4.15 (d, 2H), 5.5-5.9 (m, 3H), 7.0-7.4 (m, 5H) **2b**: $^{19}F$ NMR, -84 (t, 3F) and -117 (q, 2F); $^1H$ NMR, δ 1.70 (d, 3H), 2.4-2.8 (m, 4H), 4.15 (d, 2H),5.5-5.9 (m, 3H), 7.0-7.4 (m, 5H).
12. GLC analyses of **3a** and **3b** ($R^2$=$CH_2CH_2Ph$) showed an essentially single peak and their $^1H$ and $^{19}F$ NMR spectra also showed an essentially single set of signals, suggesting that the Claisen rearrangements proceed with a high stereospecificity. **3a**: $^{19}F$ NMR ($CDCl_3$, $CFCl_3$), -80 ppm (s); $^1H$ NMR ($CDCl_3$, TMS), δ 1.10 (d, 3H), 1.9-2.1 (m, 2H), 2.4-2.6 (m, 3H), 2.9-3.1 (m, 1H), 5.10 (d,d, 2H), 5.5-5.8 (m, 1H), 7.0-7.3 (m, 5H). **3b**: $^{19}F$ NMR, -82.6 (t, 3F) and -122.8 (q, 2F); $^1H$ NMR, δ 1.10 (d, 3H), 1.9-2.1(m, 2H), 2.4-2.6 (m, 3H), 2.9-3.1 (m, 1H), 5.10 (d,d, 2H), 5.6-5.8 (m, 1H), 7.0-7.3 (m, 5H).
13. Review on the Claisen rearrangement: Ziegler, F. E. *Chem Rev.* **1988**, *88*, 1423.
14. The kinetic experiments were made in $CDCl_3$ solutions in the range of 50-70 °C by means of $^{19}F$ NMR spectroscopy.
15. Qian, C.-P.; Nakai, T.; Dixon, D. A.; Smart, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 4602.


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