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SYNTHETIC UTILITY OF A FLUORINE-FACILITATED CLAISEN REARRANGEMENT: A NOVEL SYNTHETIC METHOD FOR 2,4-ALKADIENOIC ACIDS USING 2,2,2-TRIFLUOROETHYL PHENYL SULFOXIDE[1)]

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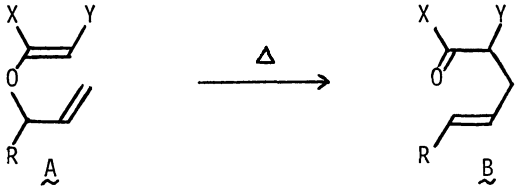
A novel synthetic method for 2,4-alkadienoic acids from allylic alcohols and 2,2,2-trifluoroethyl phenyl sulfoxide is described which involves the in situ Claisen rearrangement facilitated by the fluorine. This method was applied to the stereocontrolled synthesis of pellitorine, a natural insecticide.

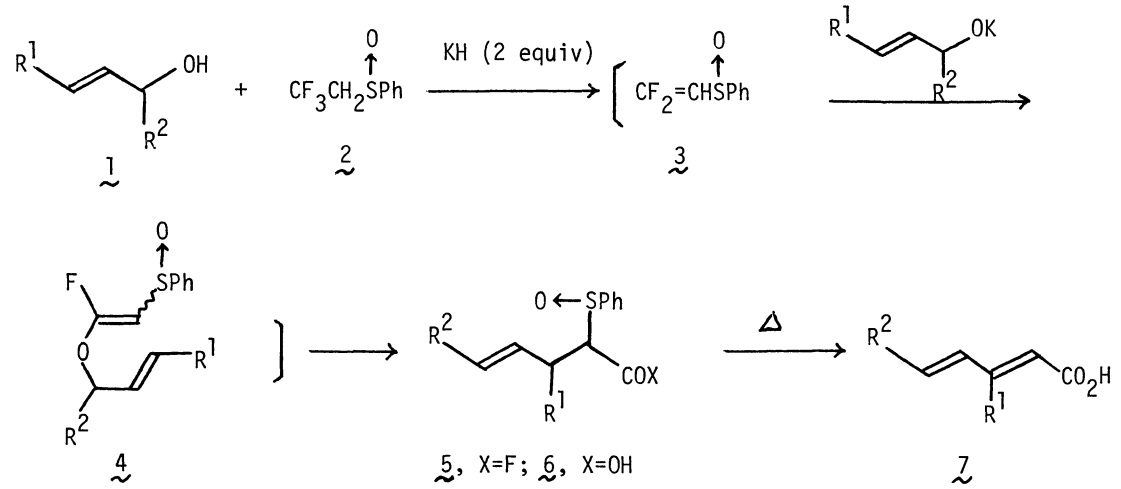
Over the years the Claisen rearrangement has proved to be exceedingly useful for the stereoselective construction of unsaturated systems (eq 1).[3)] Recently Normant and co-workers[4)] have shown that the presence of fluorine at the α-position on the vinylic part (*i.e.*, X=F in A) markedly facilitates the [3,3]sigmatropic shift; for example, a trifluorovinylic system undergoes the rearrangement at -50°C. In view of the fact that such α-fluorovinylic systems might readily be derived via the reaction of *gem*-difluoroolefins and allylic alcoholate ions, this rearrangement should provide an unique opportunity to devise new synthetic reactions.



(1)

In our continuing investigation of new applications of organofluorine reagents in *fluorine-free* organic synthesis,[5)] we now wish to report a novel synthetic method for 2,4-alkadienoic acids (7)[6)] which relies upon the fluorine-facilitated Claisen rearrangement of the particular system A (X=F and Y=SOPh) generated in situ from allylic alcohols (1) and 2,2,2-trifluoroethyl phenyl sulfoxide (2).[7)] The complete transformation is depicted in Scheme I. It should be noted here that the one-pot conversion of an alcohol (1) to the acid fluoride (5) involves the three consecutive reactions: the elimination of HF from 2, the addition-elimination reaction of the *gem*-difluoroolefin intermediate (3) with the alcoholate ion, and the spontaneous Claisen rearrangement of the α-fluorovinylic ether (4) thus generated. Therefore, the synthetic sequence consists

Scheme I



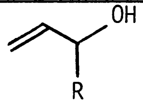
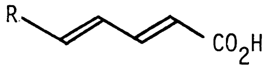
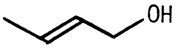
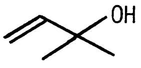
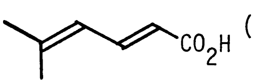
of only three operations requiring no purifications of intermediates.

Representative examples are given in Table 1. A notable feature of the present method is that secondary allylic alcohols 1 (R^1=H, R^2=alkyl) eventually afford the corresponding (2*E*, 4*E*)-alkadienoic acids (entries 2-4). In these cases, the *E* geometry of the γ,δ- and α,β-olefinic bond is established in virtue of the high stereoselectivity generally observed in the Claisen rearrangement[3] and in thermolysis of sulfoxides.[8] Unfortunately, however, (*E*)-crotyl alcohol afforded a 1 : 1 mixture of the (*E*)- and (*Z*)-isomers (entry 5) apparently as a result of the lack of stereoselectivity with regard to the vicinal chiral centers created by this Claisen variant.[9]

A typical procedure is as follows. The sulfoxide 2 was added dropwise to a previously-prepared suspension of the potassium alcoholate of 1 and potassium hydride (1.0 equiv)[10] in THF at 0-5°C over 0.5-2 h. Hydrolysis of the resulting mixture with 10% aqueous sodium hydroxide at room temperatue followed by acidification gave the acid 6. Thermolysis of 6 in refluxing chloroform or carbon tetrachloride in the presence of calcium carbonate gave rise to the dienoic acid 7. Notably, a similar thermolysis in refluxing toluene not only resulted in partial isomerization of the geometry of the γ,δ-olefinic bond, but also slightly decreased the overall yields (entries 1 and 3).

As an example of the synthetic utility of the present method, we carried out the stereocontrolled synthesis of pellitorine (8), a naturally occurring insecticide isolated from *Anacyclus pyrethrum* roots.[11] While (2*E*, 4*E*)-decadienoic acid obtained above (entry 4) was reported to serve as a good precursor of 8,[12] we have now adopted a different route (Scheme II) to the avoid above-mentioned complications encountered in the thermolytic step. Thus the acid intermediate (6a) obtained via the reaction of 1-octen-3-ol with 2 was best converted to the *N*-isobutylamide (9)[13] according to the procedure reported by Shioiri.[14] Thermolysis of 9 in refluxing toluene for 14 h followed by column chromatography (alumina) afforded the desired amide 8[15] in 55% overall

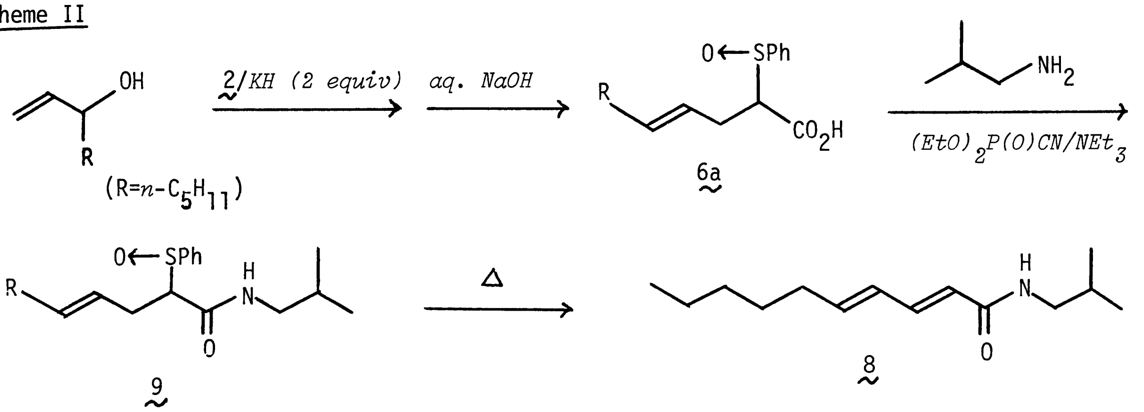
Table 1

Entry	Allylic alcohol	Solvent used for thermolysis[a]	2,4-Alkadienoic acid[b] (Overall yield,%)[c]	Stereochemical outcome[d]
				
1	$R=CH_3$	$C_6H_5CH_3$	$R=CH_3$ (55)	(2*E*,4*E*)/(2*E*,4*Z*)= 88 : 12
2	$R=CH_3$	$CHCl_3$	$R=CH_3$ (75)	(2*E*,4*E*), > 95%[e]
3	$R=n\text{-}C_5H_{11}$	$C_6H_5CH_3$	$R=n\text{-}C_5H_{11}$ (38)	(2*E*,4*E*)/(2*E*,4*Z*)= 90 : 10
4	$R=n\text{-}C_5H_{11}$	CCl_4	$R=n\text{-}C_5H_{11}$ (42)	(2*E*,4*E*), > 95%[e]
5		$CHCl_3$	 (31)	(2*E*)/(2*Z*)= 55 :45
6		$C_6H_5CH_3$	 (37)	(2*E*), >95%[e]

[a] All the thermolyses were run in the presence of calcium carbonate (1.0-1.5 equiv); otherwise, partial isomerization of the olefinic geometry occurred. Thermolysis usually took 15-20 h in refluxing toluene and 30-35 h in refluxing chloroform or carbon tetrachloride. [b] Fully characterized by spectral (ir and nmr) data. [c] Based on the alcohol used (not optimized). [d] Determined by nmr analysis. [e] This means that other stereoisomers were detected in nmr spectra.

yield from 6a. The nmr spectrum of the conjugated amide (8) thus obtained showed that the two olefinic bonds possess exclusively the *E* geometry.

Scheme II



In summary, we have now demonstrated that the facile Claisen rearrangement of the α-fluoro-β-sulfinylvinylic ether system (4) generated in situ from allylic alcohols and the trifluoroethyl sulfide (2) provides a novel synthetic method for conjugated dienoic acids (7). Thus this work not only presents the first example of synthetic applicability of fluorine-facilitated Claisen rearrangements but also illustrates the synthetic potential of organofluorine reagents in *fluorine-free* organic synthesis.

References

1) Part IX on "Applications of Organofluorine Reagents in General Organic Synthesis." Part VIII: ref 5. This work was supported in part by a Grnat-in-Aid for Scientific Research (to T. N. and N. I.) from Ministry of Education.

2) Present address: Department of Industrial Chemistry, Seikei University, Musashino, Tokyo 180.

3) Reviews:G. B. Bennett, *Synthesis*, 1978, 589; F. E. Ziegler, *Acc. Chem. Res.*, 10, 227 (1977); S. J. Rhoads and N. R. Raulins, *Org. React.*, 22, 1 (1975).

4) J. F. Normant, O. Reboul, R. Sauvètre, H. Deshayes, D. Masure, and J. Villieras, *Bull. Soc. Chim. Fr.*, 1974, 2072.

5) S. Hayashi, T. Nakai, and N. Ishikawa, *Chem. Lett.*, 1980, 935, and our earlier papers cited therein.

6) For leading references of previous methods for 2,4-alkadienoic acid derivatives, see: T. Nakai, K. Mikami, S. Taya, Y. Kimura, and T. Mimura, *Tetrahedron Lett.*, 22, 69 (1981). For more recent ones, see: K. Tanaka, M. Terauchi, and A. Kaji, *Chem. Lett.*, 1981, 315; Y. Tamura, H.-D. Choi, H. Maeda, and H. Ishibashi, *Tetrahedron Lett.*, 22, 1343 (1981).

7) Prepared in 86% yield via oxidation of CF_3CH_2SPh with sodium metaperiodate: mp 84.5-85.0°C (CCl_4); nmr ($CDCl_3$, TMS), δ 3.20-3.80 (m, $\underline{AB}X_3$, 2H) and 7.50-7.80 (m, 5H). For syntheitc utilities of the sulfide, see: K. Tanaka, S. Shiraishi, T. Nakai, and N. Ishikawa, *Tetrahedron Lett.*, 1978, 3103, and references cited therein.

8) Review: B. M. Trost, *Chem. Rev.*, 78, 363 (1978). It has been well established that thermolysis of sulfoxides proceeds exclusively in a *syn*-elimination fashion.

9) This non-diastereoselectivity is in stark contrast to the high degree of diastereoselection reported for ynamine-Claisen variants: P. A. Bartlett and W. F. Hahne, *J. Org. Chem.*, 44, 882 (1979); T. Nakai and H. Setoi, The 26th IUPAC Congress, Tokyo, 1977, Abstract IV, p. 1055 (Submitted for publication).

10) The use of sodium hydride in place of potassium hydride gave unsatisfactory results.

11) M. Jacobson, "Naturally Occurring Insecticides," M. Jacobson and D. G. Cosby, Ed., Marcel Decker, New York, 1971, p.137.

12) L. Crombie, *J. Chem. Soc.*, 1955, 999, 1007.

13) Needless to say, we attempted to obtain the amide 9 directly from the acid fluoride generated by the rearrangement; however, these attempts gave unsatisfactory results.

14) S. Yamada, Y. Kasai, and T. Shioiri, *Tetrahedron Lett.*, 1973, 1595.

15) Mp 87-89°C (Lit.[12] 90°C); nmr (CCl_4, TMS), δ 0.70-1.10 (br. d, 9H), 1.10-2.35 (m, 9H), 3.10 (t, 2H), 5.60-6.15 (m, 3H), 6.90-7.40 (m, 1H). The spectral data is in agreement with the reported values: T. Mandai, J. Gotoh, J. Otera, and M. Kawada, *Chem. Lett.*, 1980, 313.

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