

Review

[3,3]-Sigmatropic rearrangements of fluorocarbanions

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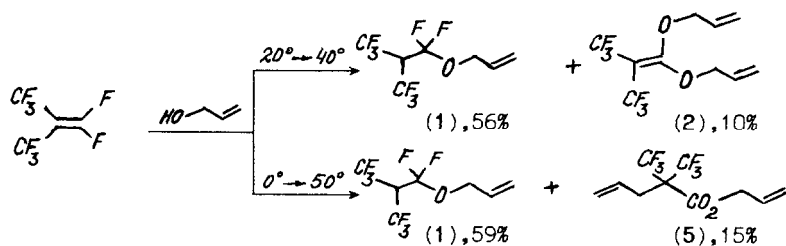
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Abstract

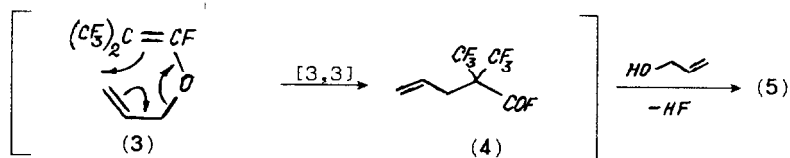
The reactions of terminal polyfluoroalkenes with 2,3-unsaturated alcohols and deprotonation of the addition products of these reagents under mild conditions give unsaturated fluoroaliphatic acids and their derivatives. The cause of the unusually mild conditions of formation of these compounds is spontaneous [3,3]-sigmatropic rearrangement of the initially formed fluorocarbanions associated with elimination of the fluoride ion. The probability of realizing sigmatropic shifts is determined by the structural peculiarities of the intermediates generated.

In recent years, [3,3]-sigmatropic rearrangements, mainly the Claisen and Ireland rearrangements, have gained increasing significance in the synthesis of various aliphatic organofluorine compounds [1]. This increasing interest is related with peculiar electron effects of fluoro and fluoroalkyl substituents whose presence in the reacting molecules facilitates the process to such an extent that the reaction, in contrast to the classical Claisen rearrangement [2], can be performed at quite low temperatures and in the absence of any catalysts.

The peculiar features of [3,3]-sigmatropic rearrangements of fluorine-containing intermediates and, in many cases, the impossibility of isolating these intermediates, led initially to the incorrect identification of the first fluoroaliphatic product of the rearrangement, which was obtained as early as 1957. The work of Koshar *et al.* [3] demonstrated that the reaction of perfluoroisobutylene (PFIB) with allyl alcohol led to the formation of two compounds: the addition product – allyl 2*H*-octafluoroisobutyl ether (1) as the major compound and a minor product, which, according to the authors corresponded to *O,O*-diallyl bis(trifluoromethyl)ketene acetal (2).



It was not until 1967 that Krespan [4] showed that the by-product of the reaction is not the ketene acetal (2) but the allyl 2,2-bis(trifluoromethyl)-pent-4-enoate (5). He explained its formation in terms of a Claisen rearrangement of the initially formed allyl heptafluoroisobutenyl ether (3) followed by further transformation of the acid fluoride 4 thus obtained, under the reaction conditions.

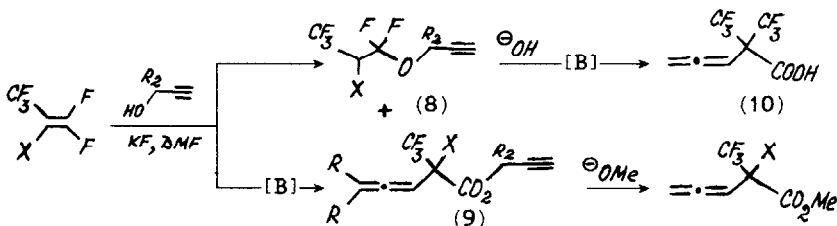


Later, the studies of Soviet [5, 6] and French [7, 8] workers demonstrated a few examples of the Claisen rearrangement proceeding under very mild conditions, including reactions of some fluorinated alkenes with allyl alcohol and dehydrofluorination reactions through the action of butyllithium on the adducts of trifluorochloroethene with allylic alcohols [7, 8].

A systematic study of the reactions of terminal perfluoroalkenes and their highly electrophilic functional derivatives with 2,3-unsaturated alcohols, which commenced in 1977 [9], allowed us to explain not only the abnormally mild reaction conditions for the [3,3]-sigmatropic rearrangement in the case of organofluorine reactants, but allowed this process to be developed as one of the main routes for the synthesis of 2-trifluoromethylsubstituted 4-ene, 3,4(2,4)-dienecarboxylic and alkenylmalonic acids.

It was found that the reaction of PFIB with allyl and crotyl alcohols was strongly influenced by the presence in the reaction medium of hydrogen fluoride acceptors and by the nature of solvent. In the presence of potassium fluoride in protophilic solvents (DMF, DMSO, HMPA), compound 5 was formed as the main product (the respective yield being ~70%); in this case the rearrangement proceeded even at -30 °C at such a high rate that the reaction kinetics could not be measured using conventional instrumental methods such as ¹⁹F NMR spectroscopy. Under similar conditions (KF/DMF, 5–20 °C), the rearrangements products 5 also occurred in the reaction of allyl alcohol with perfluoropropylene [9] and 2-methylthiopentafluoropropene [10].

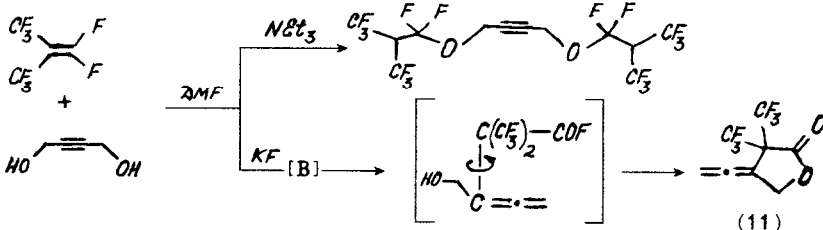
the presence of KF, the reactions took place at -10°C to 0°C ; the respective [3,3]-sigmatropic rearrangement of the intermediate fluorocarbanion **B** was accompanied by intramolecular inversion of the propargyl group, leading to the formation, of 2-trifluoromethylpenta-3,4-dienoates (**9**) (yield up to 60%), together with the addition products **8** [9, 12].



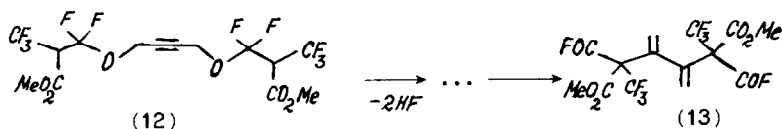
where $\text{X}=\text{F}, \text{CF}_3$; $\text{R}=\text{H}, \text{Me}$.

By analogy with the allylic ethers **1**, the propargyl ether **8**, $\text{X}=\text{CF}_3$, $\text{R}=\text{H}$ was readily transformed by KOH into 2,2-bis(trifluoromethyl)penta-3,4-dienoic acid (**10**) (yield 54%) [13].

The transformations of the fluorocarbanion **B** were shown to be notably influenced by the conditions of fluoride ion elimination [9, 12]. Thus, if the reaction of PFIB with 2-butyne-1,4-diol in DMF was performed in the presence of catalytic amounts of triethylamine, then the fluorocarbanion **B** was stabilized exclusively via proton addition. However, if an excess amount of KF was used, then rearrangement of **B** occurred leading to the formation of 2,2-bis(trifluoromethyl)-3-vinylidene-4-butanolide (**11**).

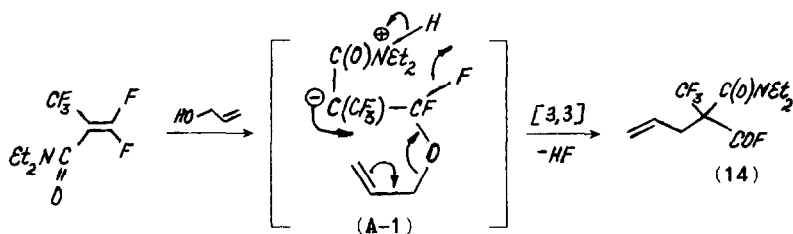


The mild conditions for the above reactions allowed us to realize an easy consecutive [3,3]-sigmatropic rearrangement, the starting compound for the reaction being an adduct of methyl perfluoromethacrylate with 2-butyne-1,4-diol (**12**). Heating **12** with complex $\text{BF}_3 \cdot \text{NEt}_3$ at 85°C gave a stable 2,5-bis(carbomethoxy)-2,5-bis(trifluoromethyl)-3,4-bis(methylene)-hexane-1,6-dioic acid difluoride (**13**) (yield 34%); this compound was presumably formed as a result of two consecutive [3,3]-sigmatropic shifts in fluorocarbanions of type **B** [14].



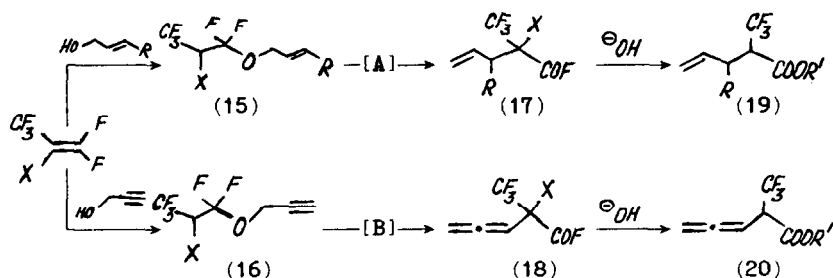
It should be pointed out that the possibility of [3,3]-sigmatropic shifts in 'polyfluoroalkenes-2,3-unsaturated alcohols' systems is influenced by the

nature of both reagents. For example, the reaction of allyl alcohol with *N,N*-diethylperfluoromethacrylamide leads exclusively to the formation of the rearrangement product of the fluorocarbanion **A-1**, i.e. the acid fluoride **14** [15].



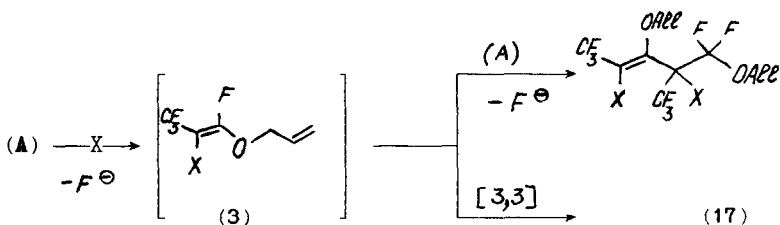
The direction of the reaction is strongly influenced by the presence of the diethylamide group which has a strong stabilizing effect on the carbanionic reaction centre [16].

Reactions of 2,3-unsaturated alcohols with highly electrophilic polyfluoroalkenes, such as methyl perfluoromethacrylate, perfluoromethacryloyl fluoride and 2-fluorosulphonylpentafluoropropene, proceed exclusively with the formation of the addition products, i.e. the 2(*X*)-2*H*-pentafluoropropyl ethers (**15**) and (**16**) which are strong CH- acids. In this case the generation of the fluorocarbanions **A** and **B** via deprotonation of the adducts **15** and **16** by the complex BF₃·NEt₃ is the most effective [9, 16, 17]. In the presence of this base the adducts **15** and **16** underwent deprotonation at 25–35 °C (X=SO₂F), 40–45 °C (X=COF) or 70–80 °C (X=CO₂Me). The resulting [3,3]-sigmatropic rearrangement of **A** or **B** proceeded almost instantaneously with high evolution of heat leading to the selective formation of the acid fluorides **17** and **18** with respective yields of 85–90% and 65–85%. Base-catalyzed hydrolysis of the acid fluorides **17** and **18** readily led to decarboxylation yielding 2-trifluoromethylpent-4-enoic (**19**) and 2-trifluoromethylpenta-3,4-dienoic (**20**) acid derivatives [18].



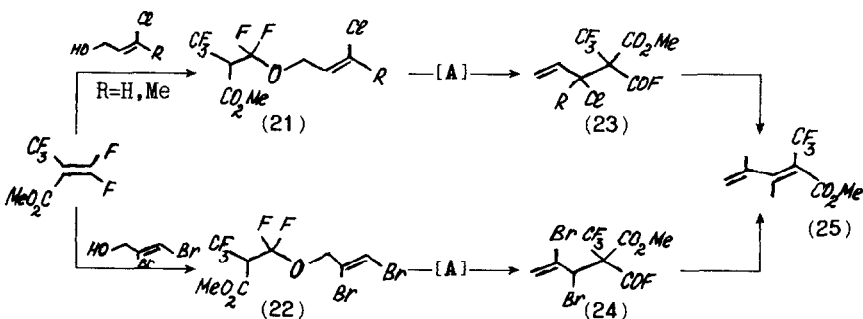
where X = CO₂Me, COF, SO₂F; R = H, Ph; R' = H, Me.

It should be emphasized that deprotonation of **15** and **16** was not accompanied by 'dimerization' side reactions of alternative allyl (propargyl) polyfluorovinyl ethers of type **3**, which is known to be quite common for reactions of this kind [19].



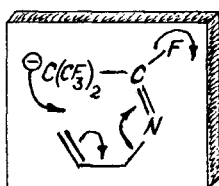
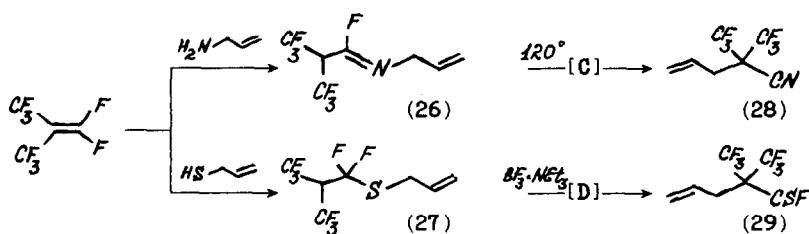
This observation is consistent with a carbanionic mechanism for the above rearrangement; indeed, where preliminary formation of ethers of type **3** occurs, their reaction with the fluorine-containing carbanions **A** or **B** would predominate.

The importance of the method of preparation of unsaturated fluoro-carboxylic acids and their derivatives, based on a [3,3]-sigmatropic rearrangement of the fluorocarbanions, is apparent in the synthesis of alkyl 2-trifluoromethylpenta-2,4-dienoates [20]. These 3-halogen-substituted allylic alcohols have been used as starting materials in reactions with methyl perfluoromethacrylate. In this case deprotonation of the adducts **21** and **22** by $\text{BF}_3 \cdot \text{NEt}_3$ at 85–110 °C proceeded with formation of the rearrangement products, i.e. the respective carboxylic acid fluorides **23** and **24**, the reaction yield being 75–90%.

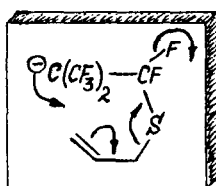


The rearrangement led to a shift of the halo-substituent from the vinyl to the allyl position, and as a result mild hydrolysis of **23** and **24** allowed us to obtain the methyl 2-trifluoromethylpenta-2,4-dienoates (**25**) via a one-stage process with a yield up to 85%.

The 'allyl' component in [3,3]-sigmatropic rearrangements also has a considerable influence on the reactivity of the fluorocarbanions. Thus, the reactions of PFIB with allylamine [21] and allyl mercaptan [22] led mainly to the formation of the addition products **26** and **27** without any dependence on the reaction conditions. Amino and thio [3,3]-sigmatropic rearrangements of fluorocarbanions **C** and **D** could only be accomplished by deprotonation of **26** and **27**; respective processes which terminated in the formation of 2,2-bis(trifluoromethyl)pent-4-enoic acid nitrile (**28**) and 2,2-bis(trifluoromethyl)pent-4-enethioyl fluoride (**29**), with respective yields of 53% and 70%.

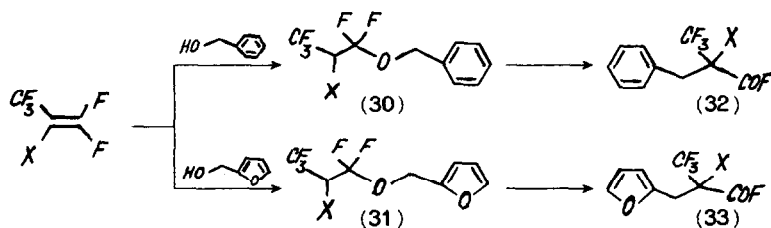


(C)



(D)

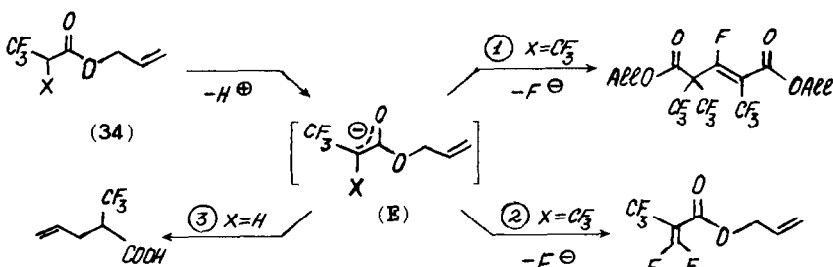
The rearrangement gives unexpected results if the allyl group is a part of an aromatic system. Thus, reactions of methyl perfluoromethacrylate and perfluoromethacryloyl fluoride with benzyl and furfuryl alcohols led to the formation of the very unstable addition products **30** and **31**. Treatment of these products with $BF_3 \cdot NEt_3$ yielded the acid fluorides **32** and **33** which were assumed to be formed not through a [3,3]-sigmatropic rearrangement, but rather by means of a [1,3]-benzyl (or furfuryl) shift.



where $X = CO_2Me, COF$

The reactions probably proceed according to a radical mechanism [23, 24]; further studies are necessary in this field to clarify the situation.

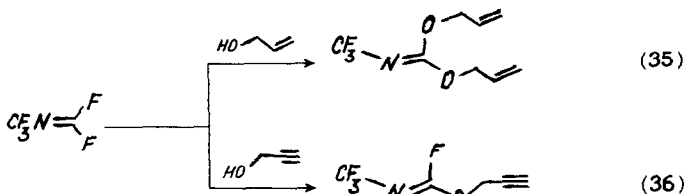
On the other hand, the possibility of a [3,3]-sigmatropic shift in the carbanions generated is strongly influenced by the electronic structure of the 'vinyl' fragment. Thus, the presence of a difluoromethylene group supposedly facilitated elimination of the fluoride ion during the rearrangement of **A** or **B**. In the absence of this group, and when two trifluoromethyl groups are present on the carbanionic centre, the sigmatropic shift is hindered. For example, the ambident fluorocarbanion **E** generated from allyl 2*H*-hexafluoroisobutyrate (**34**, $X = CF_3$) does not rearrange but is stabilized through the elimination of the fluoride ion from one of the trifluoromethyl groups.



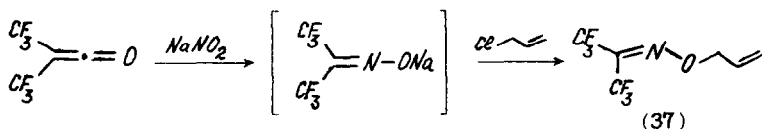
where (1) corresponds to $\text{NEt}_3/\text{Me}_3\text{SiCl}$; (2) to $\text{BF}_3 \cdot \text{NEt}_3$; and (3) to $\text{NEt}_3/\text{Me}_3\text{SiOTf}$.

However, as demonstrated by Yokozawa *et al.* [25], the allyl trifluoropropionate (**34**, $\text{X}=\text{H}$) which is capable of forming a more stable ester enolate, rearranged after treatment with an equimolar mixture of triethylamine and trimethylsilyl triflate to yield 2-trifluoromethylpent-4-enoic acid.

The electronic balance of the reactant molecule may also be affected by the presence of heteroatoms such as nitrogen. Thus, the reaction of perfluoro-2-azapropene with allyl and propargyl alcohols led to the formation of stable (up to 150°C) perfluoro-2-azapropenyl ethers (**35**) and (**36**) [26].

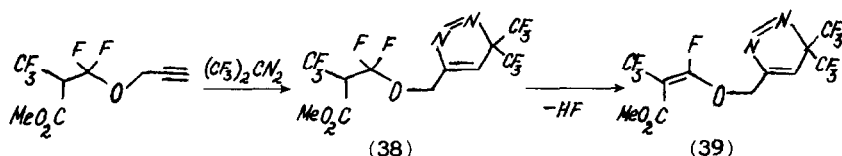


The *O*-allyl ether of hexafluoroacetoneoxime (**37**) also proved to be very stable with respect to the rearrangement [26].



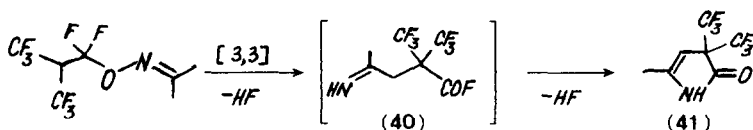
It is possible that rearrangement of the ethers **35**–**37** was hindered by very weak π -donor properties of the 'vinyl' azomethinic bond.

The 'allyl' C–N bond possesses more complex reactivity. The adduct of propargyl 2-carbomethoxy-2*H*-pentafluoropropyl ether and hexafluorodiazopropane (**38**) underwent dehydrofluorination yielding the tetrafluoropropenyl ether (**39**) exclusively.

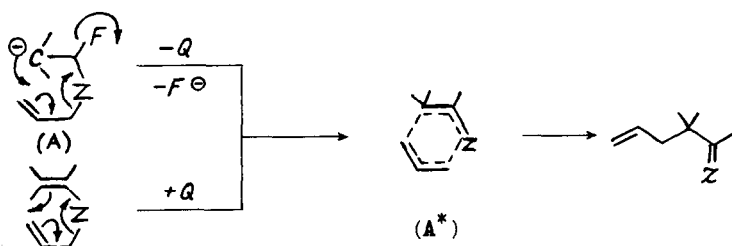


However, Zeifman *et al.* [27] found that dehydrofluorination of an *O*-(2*H*-octafluoroisobutyl)oxime even at 20°C resulted in rearrangement, the

product of the reaction being the acid fluoride **40** which, in turn, underwent cyclization yielding fluorine-containing pyrrolinone (**41**).



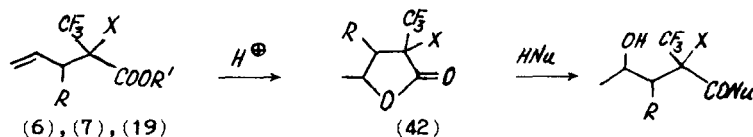
Thus, the unusually mild conditions for the [3,3]-sigmatropic rearrangement of organofluorine compounds can be logically explained in terms of the isomerization of the initially formed fluorine-containing carbanions of type **A** which are susceptible to spontaneous stabilization with the formation of a quasi-aromatic transition state **A*** which yields the rearrangement products.



where Z = O, NH or S.

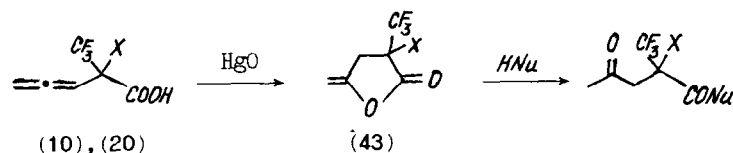
The rearrangement of **A** proceeds most readily when the molecule simultaneously contains two substituents with strong $-E$ effects on the reaction centre. Hence the rearrangement of fluorocarbanions, in contrast to the classical Claisen rearrangement [2], is very rapid and exothermic. Such data are consistent with the calculations of Evans and Golob [28], who demonstrated that the [3,3]-sigmatropic shift rate is 10^{10} – 10^{17} times higher if the reaction intermediate is in the ionic form, as well as with the results of Denmark and Harmata [29] relating to carbanion-accelerated Claisen rearrangements. Probably, the stronger n - π interactions in the fluorocarbanion **A**, in comparison to the π - π interactions in the classical variants, lead to a greater ordering of the system in the initial state and a substantial reduction in the activation energy of the process **A** \rightarrow **A***. One of the possible trends of a further study of the carbanionic mechanism could be an investigation of the interaction of stable allyl (propargyl) polyfluorovinyl ethers with the fluoride ion.

The rearrangement products are valuable synthons for various CF₃-substituted compounds. Thus, pent-4-enoic acids and their methyl esters (**6**, **7**, **19**) readily undergo cyclization yielding 2-trifluoromethyl-4-methyl-4-butanolides (**42**) [11, 18, 30], which, in turn, could be used as acylating agents in reactions with nucleophiles yielding fluorine-containing derivatives of 4-oxypentanoic acids.



where $X = H, F, CF_3, SCH_3$; $R = H, Me, Ph$; $R' = H, Me$.

Cyclocondensation of the penta-3,4-dienoic acids (10) and (20) leads to the formation of 2-trifluoromethyl-4-methylene-4-butanolides (43) [13, 18], which readily acylate various nucleophiles yielding fluorine-containing derivatives of levulinic acid.



where $X = H, CF_3$.

The unsaturated fluoroaliphatic acids (6, 7, 10, 19, 20) could be used in reactions with dipolarophiles, dienes and heterodienes, as well as in heterocyclization reactions, thus enabling a wide range of practically valuable compounds to be obtained.

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