A new approach to the synthesis of trifluoromethylated products of the [3,3]-sigmatropic rearrangement

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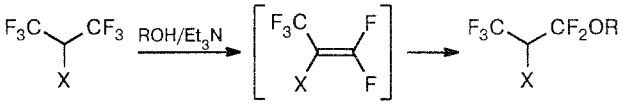
CH-acids of general formula $CF_3CH(X)CF_3$ (X = CF_3, CO_2R) react with 2,3-unsaturated alcohols in the presence of bases to give trifluoromethylated products of the [3,3]-sigmatropic rearrangement. These reactions provide a convenient method for the synthesis of 2-alkenyl-2-trifluoromethylmalonates.

Key words: CH-acids, fluorinated; [3,3]-sigmatropic rearrangement; 2-alkenyl-2-trifluoromethylmalonates.

[3,3]-Sigmatropic rearrangements provide an efficient method for the formation of a new C—C bond in fluorine-containing aromatic and aliphatic systems.[1] A number of low-temperature syntheses of various derivatives of unsaturated fluorocarboxylic acids,[1,2] including those of trifluoro-substituted acids,[3] have been elaborated using these rearrangements as the key reactions. The most convenient method for the synthesis of the latter derivatives, *e.g.*, acid fluorides and acids (**4**), involves deprotonation of allyl 2*X*-2*H*-pentafluoropropanates (**3**),[3] whose precursors [polyfluoroalkenes (**2**)] are obtained from fluorinated CH-acids (**1**) (Scheme 1).

Unsaturated synthons **4** are valuable intermediates for the syntheses of various CF_3-substituted compounds including esters (**5**). However, the fact that the syntheses of polyfluoroalkenes **2** and the unstable adducts **3** are rather laborious calls for a search for simpler and more convenient approaches to the preparative synthesis of fluorine-containing rearrangement products. Of these methods, the one-step synthesis of esters **5** directly from CH-acids **1** without isolation of compounds **2** and **3** is likely to be the most suitable approach.

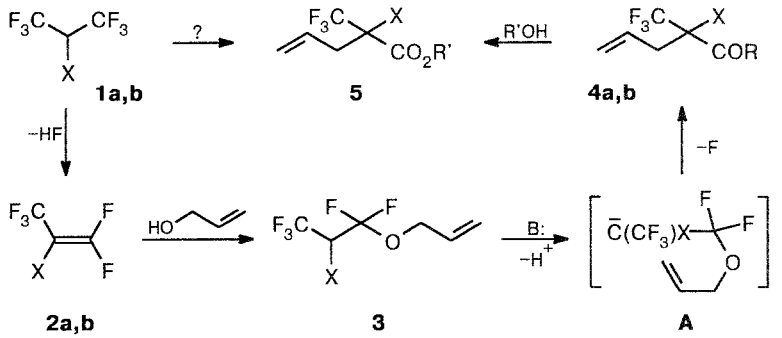
Previously, the "partial saponification of the trifluoromethyl group" method was developed[4,5] using 2*H*-nonafluoroisobutane **1a** and 2*H*-hexafluoroisobutyrates **1b,c**. This method made it possible to obtain adducts (**6**) rather smoothly in reactions of CH-acids **1a—c** with simple alcohols in the presence of triethylamine.



1a—c **2a—c** **6**

a: X = CF_3
b: X = CO_2Me
c: X = CO_2Et
R = Me, Et

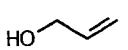
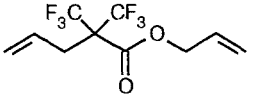
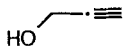
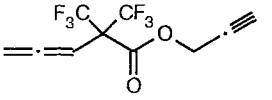
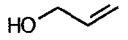
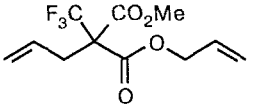
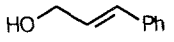
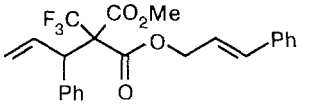
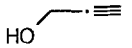
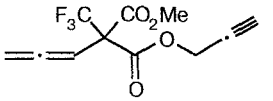
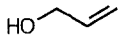
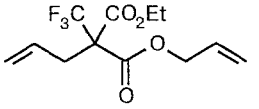
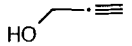
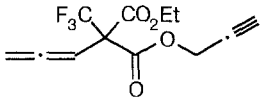
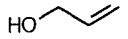
Scheme 1



a: X = CF_3, R = OH, B: = KOH
b: X = CO_2Me, R = F, B: = $Et_3N \cdot BF_3$
R' = Alk

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1273—1277, July, 1994.

Table 1. Interaction of fluorinated CH-acids **1** with 2,3-unsaturated alcohols in the presence of bases

CH-acid $CF_3CH(X)CF_3$	X	2,3-Unsaturated alcohol	Base	Main rearrangement product	
1a	CF_3		Et_3N		(7)
1a	CF_3		Et_3N		(8)
1b	CO_2Me		$Et_3N \cdot BF_3$		(12)
1b	CO_2Me		$Et_3N \cdot BF_3$		(13)
1b	CO_2Me		$Et_3N \cdot BF_3$		(17)
1c	CO_2Et		$Et_3N \cdot BF_3$		(14)
1c	CO_2Et		$Et_3N \cdot BF_3$		(18)
1d	COOH		$Et_3N \cdot BF_3$	—	—

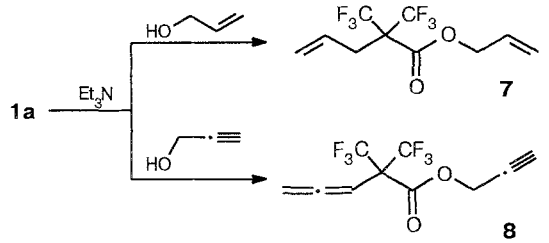
It was not obvious before the present work that this approach is promising for reactions **1** → **5**, since the question remained open: is it possible to implement smoothly the key steps of the processes (*i.e.*, the generation and [3,3]-sigmatropic rearrangement of the intermediate carbanion **A**) *in situ* during the consecutive transformations **1** → **5**, which are probably complicated by side reactions?

To answer this question, we studied the reactions of fluorinated CH-acids **1** with 2,3-unsaturated alcohols in the presence of bases (Table 1).

It turned out that under standard conditions[4] (Et_3N, 25—30 h at 100 °C) 2*H*-nonafluoroisobutane **1a** reacts with allyl alcohol to give a complex mixture of compounds. The rearrangement product, allyl 2,2-bis(trifluoromethyl)-4-pentenoate (**7**), was isolated in 12 % yield from this mixture (Scheme 2).

The reaction of compound **1a** with propargyl alcohol also proceeds ambiguously. The resulting rearrangement product, propargyl 2,2-bis(trifluoromethyl)-3,4-pentadienoate (**8**), was isolated in 9 % yield. Probably, the yields of esters **7** and **8*** are low due to the low CH-acidity

Scheme 2



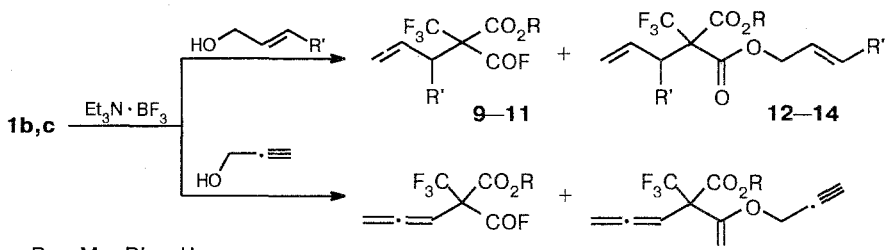
of reagent **1a** (*cf.* Ref. 8), which makes it necessary to use drastic reaction conditions and a strong organic base (Et_3N), causing oligomerization of the starting unsaturated alcohols.

If the CH-acids used contain groups capable of conjugation with the intermediate carbanionic center,[9] the transformations studied occur much more easily.

For example, 2*H*-hexafluoroisobutyrates **1b,c** react exothermically with 2,3-unsaturated alcohols under the conditions reported previously[4,5] (Et_3N, without a solvent) to give mixtures of products that are difficult to separate. However, esters **1b,c** readily react with allyl, cinnamic, and propargyl alcohols with slight heating in the presence of the $Et_3N \cdot BF_3$ complex in an aprotic solvent to give mixtures of rearrangement products, acyl fluorides (**9—11**, **15**, **16**) (yields up to 15 %), and the

* The rearrangement products **7** and **8** were also obtained in preparative yields from reactions of allyl and propargyl alcohols with perfluoroisobutylene.[6,7]

Scheme 3



9, 12: R = Me, R' = H
10, 13: R = Me, R' = Ph
11, 14: R = Et, R' = H
15, 17: R = Me
16, 18: R = Et

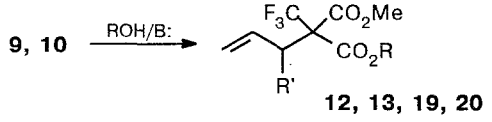
corresponding diesters of 2-trifluoromethyl-substituted 2-(2-propenyl)- (**12**, **14**), 2-(1-phenyl-2-propenyl)- (**13**), and 2-allenylmalonic acids (**17**, **18**) (yields up to 75 %) (Scheme 3).

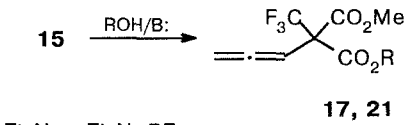
These reactions proceed at high rates and evolve much heat, and hence they have to be carried out in solvents. Benzene proved to be the most suitable solvent. In benzene the reactions start at 55—65 °C and are completed in 30—40 min. It should be emphasized that the rate-determining step involves the interaction of the acyl fluorides that result from the [3,3]-sigmatropic rearrangement with the starting 2,3-unsaturated alcohols. Therefore, the reaction time increases to 8 h in the case of acyl fluoride **10** due to the strong steric effect of the phenyl group.

We also obtained trifluoromethylated alkenylmalonates in up to 90 % yields by the alcoholysis of acyl fluorides **9**, **10**, and **15** (Scheme 4) synthesized according to the known procedure.[10]

The hitherto unknown acyl fluoride **10** was obtained in 67 % yield by *in situ* deprotonation of the very unstable cinnamyl ester **22**, which was initially formed in the reaction of methyl perfluoromethacrylate **2b** with cinnamic alcohol. The hydrolysis of acyl fluoride **10** and that of its analogs **9** and **15** (*cf.* Ref. 11) was accompanied by decarboxylation and the transformation of the malonic system into ester **23** (Scheme 5).

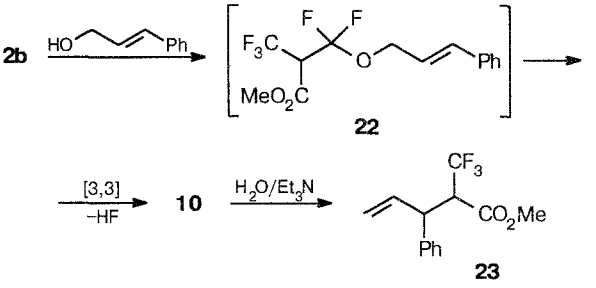
Scheme 4





B: = Et_3N or $Et_3N \cdot BF_3$
12: R = $CH_2CH{=}CH_2$, R' = H
13: R = $CH_2CH{=}CHPh$, R' = Ph
17: R = $CH_2C{\equiv}CH$
19: R = Et, R' = H
20: R = Me, R' = Ph
21: R = Et

Scheme 5



An attempt to obtain the rearrangement product in the reaction of 2*H*-hexafluoroisobutyric acid (**1d**) with allyl alcohol was unsuccessful: when this acid was heated with $Et_3N \cdot BF_3$, it decomposed to give gaseous products. On the other hand, the rearrangement product (ester **24**) was formed in 51 % yield by treatment of the 2*H*-pentafluoropropene **2d** obtained from the acid **1d** (*cf.* Ref. 12) with allyl alcohol in the presence of $Et_3N \cdot BF_3$ and a catalytic amount of Et_3N (4 days at 25 °C) (Scheme 6).

Scheme 6

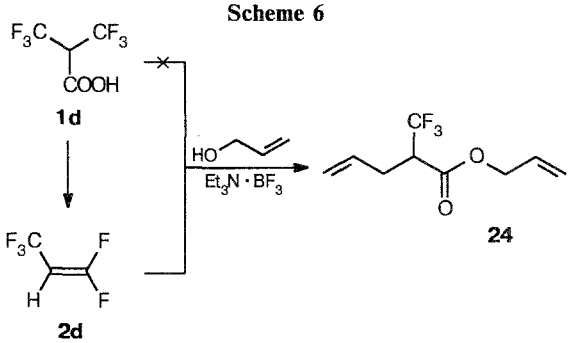


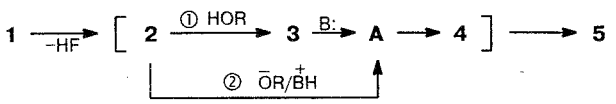
Table 2. Parameters of compounds **10—14**, **16—21**, **23**, and **24**

Compound	Yield* (%)	B.p./°C (*p*/Torr)	d_4^{22}	n_D^{22}	^{19}F NMR (C_6D_6, δ, *J*/Hz)	IR (ν/cm^{-1})	Found / Calculated (%) C	H	F	Molecular formula
10**	67	81(0.7)	—	1.4651	−13.9 (d, 10.0); −122.7 (m); −14.8 (d, 10.0); −124.9 (m)	1850 (CF=O); 1760 (C=O); 1640 (C=C); 1605 (Ph)	55.57 / 55.26	3.99 / 3.95	25.14 / 25.00	$C_{14}H_{12}F_4O_3$
11	10	67(15)	—	1.3792	−10.5 (d, 10.0); −117.1 (q, 10.0)	1845 (CF=O); 1750 (C=O); 1640 (C=C)	44.86 / 44.63	4.15 / 4.13	31.24 / 31.40	$C_9H_{10}F_4O_3$
12	73	77(2)	1.222	1.4156	−11.4 (s)	1770 and 1750 (C=O); 1655 (C=C)	49.58 / 49.62	4.90 / 4.89	21.83 / 21.43	$C_{11}H_{13}F_3O_4$
13**	58	170—190 (0.5)***	—	—	−15.9 (s); −16.0 (s)	1750 (C=O); 1640 (C=C); 1600 (Ph)	65.86 / 66.03	4.94 / 5.02	13.56 / 13.64	$C_{23}H_{21}F_3O_4$
14	65	83(2)	1.178	1.4160	−11.5 (s)	1750 and 1735 (C=O); 1640 (C=C)	51.57 / 51.43	5.28 / 5.36	20.31 / 20.36	$C_{12}H_{15}F_3O_4$
16	9	70(13)	—	1.3944	−8.2 (d, 10.0); −115.0 (q, 10.0)	1980 and 1955 (CH_2=C=CH); 1855 (CF=O); 1760 (C=O)	45.28 / 45.00	3.41 / 3.33	31.42 / 31.67	$C_9H_8F_4O_3$
17	71	84(0.7)	1.297	1.4366	−9.5 (s)	3305 and 2150 (C≡CH); 1995 and 1975 (CH_2=C=CH); 1780 and 1760 (C=O)	50.07 / 50.38	3.36 / 3.44	21.90 / 21.76	$C_{11}H_9F_3O_4$
18	63	83(0.5)	1.266	1.4372	−9.4 (s)	3310 and 2150 (C≡CH); 1990 and 1970 (CH_2=C=CH); 1765 (C=O)	52.43 / 52.17	3.96 / 3.99	20.48 / 20.65	$C_{12}H_{11}F_3O_4$
19	90	98.5(17)	1.217	1.4010	−11.4 (s)	1750 and 1735 (C=O); 1640 (C=C)	47.08 / 47.24	5.19 / 5.12	22.57 / 22.44	$C_{10}H_{13}F_3O_4$
20	81	114(0.5)	—	1.4800	−15.6 (br.s)	1750 and 1735 (C=O); 1635 (C=C); 1600 (Ph)	57.15 / 56.96	4.83 / 4.75	17.84 / 18.04	$C_{15}H_{15}F_3O_4$
21	86	71(1)	—	1.4180	−9.4 (s)	1980 and 1960 (CH_2=C=CH); 1755 and 1740 (C=O)	47.52 / 47.62	4.40 / 4.37	22.87 / 22.62	$C_{10}H_{11}F_3O_4$
23**	72	104(5)	—	1.4720	−13.8 (d, 7.5); −14.0 (d, 7.5)	1755 (C=O); 1640 (C=C); 1600 (Ph)	60.75 / 60.47	4.93 / 5.04	22.04 / 22.09	$C_{13}H_{13}F_3O_2$
24	51	81(40)	—	1.3938	−9.7 (d, 7.5)	1750 (C=O); 1645 (C=C)	51.77 / 51.92	5.32 / 5.29	27.60 / 27.40	$C_9H_{11}F_3O_2$

* Yields of diesters **12—14**, **17**, and **18** in the reactions starting from isobutyrates **1b,c**. ** As a mixture of diastereomers in the ratio 1 : 1. *** A light-yellow oil.

The new approach to the synthesis of esters of trifluoromethylated unsaturated acids **5** opens broad prospects for the one-step synthesis of various fluoroaliphatic products of the [3,3]-sigmatropic rearrangement of fluorinated CH-acids that can smoothly undergo dehydrofluorination. Taking into account that excess base is always present and that the reaction rates are high, the second transformation pathway should be considered as the most probable (Scheme 7).

Scheme 7



The choice of the base, the reaction conditions, and the yields of the final products are determined by the strength of the starting CH-acid.

The parameters of the compounds synthesized are presented in Table 2.

Experimental

^{19}F NMR spectra were recorded on a Bruker WP-200SY spectrometer (188.3 MHz) using CF_3COOH as the external standard. IR spectra were obtained on a UR-20 spectrophotometer.

Synthesis of 2-alkenyl-2-trifluoromethylmalonates (general procedures)

From alkyl 2*H*-hexafluoroisobutyrates. A mixture of butyrate **1b** (or **1c**) (25 mmol), allyl (cinnamic or propargyl) alcohol (60—65 mmol), and $Et_3N \cdot BF_3$ (80 mmol) in absolute benzene (25—30 mL) was slowly heated to 55—65 °C with stirring. When the reaction mixture became turbid (a two-phase system formed), it was refluxed for 30—40 min (or for 8 h in the case of cinnamic alcohol) with vigorous stirring and then cooled. The products were isolated as indicated below.

From methyl 2-fluoroformyl-2-trifluoromethyl-4-pentenoate and -3,4-pentadienoate. *A.* A solution of Et_3N (30 mmol) in abs. MeOH (EtOH) (5 mL) was added dropwise with stirring and cooling (5—10 °C) to a solution of acyl fluoride **9** (**10** or **15**) (15 mmol) in abs. MeOH (EtOH) (5 mL). The reaction mixture was stirred for 30 min at 40—45 °C (or refluxed for 2 h in the case of acid fluoride **10**), cooled, and concentrated *in vacuo*.

B. A solution of $Et_3N \cdot BF_3$ (30 mmol) in abs. benzene (5 mL) was added dropwise with stirring to a solution of acyl fluoride **9** (**10** or **15**) (15 mmol) and allyl (cinnamic or propargyl) alcohol (35 mmol) in abs. benzene (10 mL). The reaction mixture was refluxed for 30—40 min with stirring (or for 6 h in the case of acyl fluoride **10**) and cooled.

Methyl 2-fluoroformyl-2-trifluoromethyl-3-phenyl-4-pentenoate (10). A solution of methyl perfluoromethacrylate **2b** (8.5 g, 45 mmol) in abs. benzene (5 mL) was added dropwise with stirring and cooling (10—15 °C) to a solution of cinnamic alcohol (6.0 g, 45 mmol) in abs. benzene (5 mL). After 15 min, a solution of $Et_3N \cdot BF_3$ (9.1 g, 54 mmol) in abs. benzene (5 mL) was added. The mixture was refluxed with stirring for 30 min and cooled.

Methyl 2-trifluoromethyl-3-phenyl-4-pentenoate (23). A mixture of acyl fluoride **10** (6.1 g, 20 mmol), water (0.7 g, 40 mmol), and Et_3N (3.0 g, 30 mmol) in THF (20 mL) was refluxed for 5 h, cooled, and concentrated *in vacuo*.

Allyl 2-trifluoromethyl-4-pentenoate (24). A mixture of propene **2d** (6.7 g, 51 mmol), $Et_3N \cdot BF_3$ (17.3 g, 102 mmol), and Et_3N (0.5—1.0 mL) in allyl alcohol (15 mL) was kept in a sealed glass tube for 4 days at 25 °C.

In all of the experiments, the reaction products were isolated according to the following procedure: the reaction mixture (or the residue after concentrating) was diluted with ether (50—100 mL) and washed with acidified water (2×100 mL) and then with water (1×100 mL). The ethereal layer was dried with $MgSO_4$ and concentrated, and the residue was fractionated.

References

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