Ethyl 2-(α-hydroxyhexafluoroisopropyl)acrylate as a potential precursor of fluorine- and sulfur-containing CH-acids

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The reactivity of ethyl 2-(α-hydroxyhexafluoroisopropyl)acrylate (**1**) was studied. The addition of thioacetic acid to compound **1** occurs at 20 °C, while reactions with thiols proceed only at 120 °C and are accelerated in the presence of an acid catalyst. Dealkylation of acrylate **1** with iodotrimethylsilane affords 4,4,4-trifluoro-3-hydroxy-2-iodomethyl-3-trifluoromethylbutyric acid, which served as the starting compound for the synthesis of 3-chloro-4,4,4-trifluoro-2-iodomethyl-3-trifluoromethylbutyroyl chloride, a potential precursor of alicyclic fluorine- and sulfur-containing CH-acids.

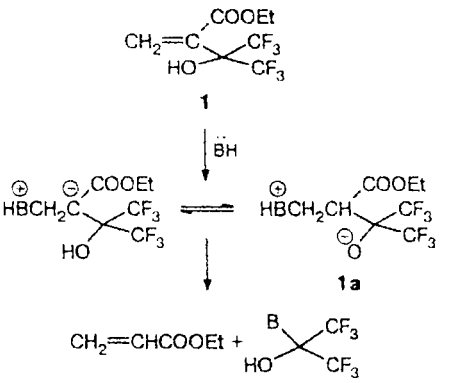
Key words: ethyl 2-(α-hydroxyhexafluoroisopropyl)acrylate, thiolation, iodotrimethylsilane, dealkylation, chlorinolysis, 4,4,4-trifluoro-3-hydroxy-2-iodomethyl-3-trifluoromethylbutyric acid, 3-chloro-4,4,4-trifluoro-2-iodomethyl-3-trifluoromethylbutyroyl chloride, ethyl 2-acetylthio- and ethyl 2-alkyl(phenyl)thiomethyl-4,4,4-trifluoro-3-hydroxy-3-trifluoromethylbutyrates.

Esters of α,β-unsaturated carboxylic acids containing α-hydroxypolyfluoroalkyl groups in the α-position became available due to the recently discovered ability of polyfluorocarbonyl compounds to alkylate acrylates and their homologs under mild conditions in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO).[1] The first results of a study of the reactivity of these compounds with ethyl 2-(α-hydroxyhexafluoroisopropyl)acrylate (**1**) as an example are given in this work. Primary attention was given to the syntheses of alicyclic fluorine- and sulfur-containing CH-acids by thiolation of acrylate **1**, as well as to the synthesis of α-polyfluoroalkyl-substituted β-haloalkanoyl chlorides, precursors of alicyclic CH-acids (see Ref. 2), from compound **1**. In addition, the behavior of **1** in the presence of strong bases, which are the most effective catalysts of β-thiolation of acrylic systems,[3] and the ability of the ester group in **1** to undergo hydrolysis and dealkylation were assessed.

It turned out that acrylate **1** was not indifferent toward bases. Even during storage in glass, it slowly dissociates into the initial compounds, hexafluoroacetone and ethyl acrylate, and readily decomposes upon treatment with aqueous alkaline solutions with complete mineralization of the C—F bonds. Decomposition of acrylate **1** is also induced by highly basic *N*-nucleophiles, probably due to the low stability of anion **1a** formed through stepwise addition of a highly basic nucleophile to the C=C bond (Scheme 1).

These assumptions are consistent with the following facts. During optimization of the synthesis of acrylate **1** from ethyl acrylate and hexafluoroacetone in the presence of DABCO, we found that the reaction equilibrium is shifted towards the formation of **1** when the temperature is decreased from 20 to 5 °C, and the conversion of the reagents and the yield of the final product increase when neutralization of DABCO is carried out with cooling. It was also shown that of *N*-nucleophiles only weakly alkaline amines, *e.g.*, morpholine, can be made to cause the β-amination of **1** with the formation of an ester of amino acid **2** (Scheme 2).

Scheme 1

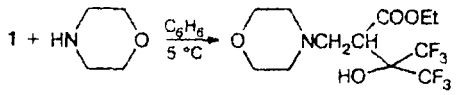


High selectivity of this reaction was reached at a high dilution of reagents and when the latter were mixed with cooling, *i.e.*, under conditions favoring the realization of the push-pull addition mechanism.

Due to decomposition of **1** in the presence of strong bases, thiolation of **1** was studied only as a noncatalytic

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 4, pp. 786—790, April, 1997.

Scheme 2

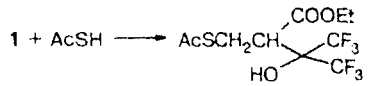


2

and an acid-catalyzed process using certain aliphatic, arylaliphatic, and aromatic thiols and thiocarboxylic acids as thiolating agents. It was shown that thiol compounds do not cause decomposition of **1** even under drastic conditions (120 °C). The characteristic feature of these reactions is their regiospecificity resulting only in β-thiolation products, both in the presence and in the absence of a catalyst. The direction of the reaction was not changed in the presence of oxygen, which is typical of similar reactions involving non-fluorinated acrylates.[3]

In the absence of a catalyst, the conditions and rate of β-thiolation of **1** are determined by the acidic properties of the thiol. For example, thioacetic acid slowly adds to the multiple bond of **1** even at 20 °C to give thioacetate **3** in 80% yield after 7 days (Scheme 3). At 100 °C, a similar result is reached after 1.5 h.

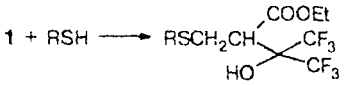
Scheme 3



3

Thiols of the aliphatic and arylaliphatic series do not react with **1** at 20 °C; thiolation occurs at a noticeable rate only at 120 °C. Under these conditions, the more acidic α-toluenethiol gives the β-thiolation product **4** in 70% yield in 20 h, and in the case of *n*-pentanethiol the yield of sulfide **5** does not exceed 50% even after 30 h (Scheme 4).

Scheme 4



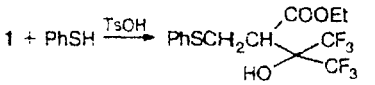
4, 5

R = $PhCH_2$ (**4**); n-C_5H_{11} (**5**)

The thiolation of **1** is significantly accelerated by acidic catalysis. For example, *n*-pentanethiol in the presence of trifluoromethanesulfonic acid (TfOH) affords sulfide **5** in 75% yield already in 7 h at 100 °C.

It should be noted that TfOH can be used as a catalyst of thiolation of **1** only for aliphatic thiols. This superacid forms strong charge transfer complexes with thiols of aromatic series, for example, benzenethiol. These complexes do not decompose under the reaction conditions, which impedes the catalytic action. In this case, the use of the weaker *p*-toluenesulfonic acid (TsOH) appeared to be effective. In the presence of TsOH, sulfide **6** was obtained in 90% yield at 120 °C in 8 h (Scheme 5).

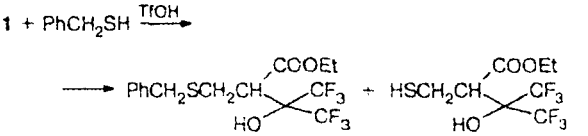
Scheme 5



6

The thiolation of acrylate **1** with α-toluenethiol is promoted by TfOH. The reaction proceeds at a high rate at 50 °C (2 h) and is accomplished in 1 h at 80 °C. However, under these conditions, TfOH catalyses debenzylation of sulfide **4** to form thiol **7** (Scheme 6), as shown by NMR and by a test for the HS group with ninhydrin.

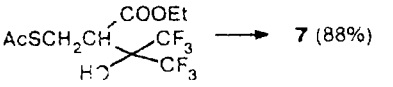
Scheme 6



4 **7**

To confirm the structure of thiol **7** isolated from the mixture of the reaction products, we synthesized this compound independently by hydrolysis of *S*-acetyl derivative **3** with HCl in methanol (20 °C, 20 h) (Scheme 7).

Scheme 7



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^1H and ^{19}F NMR spectra of the samples of **7** prepared both by deacetylation of **3** and acid-catalyzed thiolation of **1** with α-toluenethiol appeared to be identical.

The fluorine-containing CH-acids **3**—**6** synthesized are stable liquids. The ester group in these compounds does not change even upon prolonged boiling with HCl. As can be seen from the ^{19}F NMR spectra (Table 1), the CF_3 groups of **3**—**6** are diastereotopic.

It appeared to be impossible to transform acrylate **1** into acyl chloride of the corresponding β-haloalkanoic acid by usual methods.[2] Boiling with HCl and HBr does

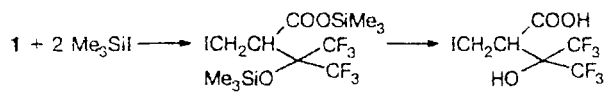
Table 1. Spectral characteristics of compounds **2**—**8** and **10**

Compound	^{1}H NMR	^{19}F NMR
	δ, *J*/Hz*	
2	0.9 (t, 3 H, Me, *J* = 7.4); 1.8 (m, 4 H); 2.25 (m, 2 H); 3.0 (m, 6 H); 3.9 (m, 1 H, CH); 9.2 (s, 1 H, OH)	−1.2 (q, 3 F, CF_3, *J* = 9.6); −3.8 (q, 3 F, CF_3, *J* = 12.8)
3	1.2 (t, 3 H, Me, *J* = 7.2); 2.2 (s, 3 H, Me); 2.9—3.2 (m, 2 H); 3.5 (m, 1 H); 4.2 (q, 2 H, CH_2, *J* = 7.5); 5.25 (s, 1 H, OH)	−2.3 (q, 3 F, CF_3, *J* = 12.0); −4.4 (q, 3 F, CF_3, *J* = 11.6)
4	1.4 (t, 3 H, Me, *J* = 7.2); 2.85 (m, 2 H); 3.2 (m, 1 H); 3.75 (s, 2 H, CH_2); 4.3 (q, 2 H, CH_2, *J* = 7.5); 5.7 (br.s, 1 H, OH); 7.3 (m, 5 H, Ph)	−2.2 (q, 3 F, CF_3, *J* = 12.0); −5.3 (q, 3 F, CF_3, *J* = 9.7)
5	0.85 (t, 3 H, Me, *J* = 7.2); 1.3 (m, 7 H); 1.6 (m, 2 H, CH_2); 2.5 (m, 2 H, CH_2); 2.9—3.2 (m, 3 H); 4.3 (q, 2 H, CH_2, *J* = 7.6); 5.6 (br.s, 1 H, OH)	−2.0 (q, 3 F, CF_3, *J* = 11.2); −5.1 (q, 3 F, CF_3, *J* = 9.7)
6	1.3 (t, 3 H, Me, *J* = 7.2); 3.2—3.5 (m, 3 H); 4.3 (q, 2 H, CH_2, *J* = 8.0); 5.7 (br.s, 1 H, OH); 7.3 (m, 5 H, Ph)	−2.3 (q, 3 F, CF_3, *J* = 9.7); −5.4 (q, 3 F, CF_3, *J* = 9.7)
7	1.3 (t, 3 H, Me, *J* = 6.5); 1.6 (t, 1 H, SH, *J* = 7.8); 2.85—3.2 (m, 3 H); 4.3 (q, 2 H, CH_2, *J* = 6.5); 5.3 (br.s, 1 H, OH)	−2.2 (q, 3 F, CF_3, *J* = 8.25); −4.9 (q, 3 F, CF_3, *J* = 10.0)
8	3.5 (m, 2 H); 3.8 (m, 1 H); 7.0 (s, 1 H, OH); 7.1 (br.s, 1 H, OH)	−2.9 (q, 3 F, CF_3, *J* = 9.6); −5.0 (q, 3 F, CF_3, *J* = 9.6)
10	3.4 (dd, 1 H, *J* = 11.0); 3.6 (m, 1 H); 4.6 (t, 1 H, CH, *J* = 8.5)	−2.0 (q, 3 F, CF_3, *J* = 8.5); −6.9 (q, 3 F, CF_3, *J* = 8.5)

*The solvents used were C_6D_6 for **2**, $CDCl_3$ for **3**—**7** and **10**, and $(CD_3)_2C{=}O$ for **8**.

not result in either hydrolysis of its ester group or hydration of the multiple bond. Acrylate **1** does not react with anhydrous HBr in CH_2Cl_2 solution in a sealed vessel even upon prolonged storage (7 days). Positive results were obtained only by heating (100 °C, 10 h) of acrylate **1** with such a strong dealkylating agent as Me_3SiI. Silylation of the hydroxy group of **1** with the liberation of HI, apparently, can initially occur under mild conditions, and heating may result in the addition of HI to the C=C bond and dealkylation of the ester group to form bis-silyl derivative **8a**. Methanolysis of **8a** (65—70 °C, 1.5 h) afforded acid **8** in 65% yield (Scheme 8).

Scheme 8

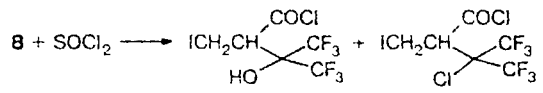


8a **8**

Treatment of acid **8** with thionyl chloride readily affords acyl chloride **9**. However, the hydroxy group simultaneously undergoes chlorolysis, which results in an inseparable mixture of acyl chlorides **9** and **10** (1 : 1) (Scheme 9).

The reaction of acid **8** with oxalyl chloride is more selective. In this case, the main product is acyl chloride **10** that was isolated in a pure state in 43% yield. Thus, acrylate **1** can be considered suitable for the syntheses of not only acyclic fluorine- and sulfur-containing

Scheme 9



9 **10**

CH-acids but precursors of their cyclic analogs and, primarily, α-polyfluoroalkylsubstituted β-thiolactones.[2]

Experimental

Anhydrous solvents were used; commercial reagents were purified before the experiments; acrylate **1** was distilled. ^{1}H and ^{19}F NMR spectra were recorded on a Bruker WP-200SY spectrometer at 200.12 and 188.31 MHz, respectively. The characteristics of new synthesized compounds **2**—**10** are given in Table 2, and the ^{1}H and ^{19}F NMR spectral parameters are given in Table 1.

Ethyl 2-(α-hydroxyhexafluoroisopropyl)acrylate (1). Ethyl acrylate (20.0 g, 0.2 mol), DABCO (2.2 g, 0.002 mol), and THF (150 mL) were placed in a glass tube, and the tube was cooled to −78 °C. Hexafluoroacetone (35.5 g, 0.22 mol) was condensed into the tube, and the tube was then sealed and kept at 20 °C for 3 days and at 5 °C for 7 days. The cooled tube was opened, the reaction mixture was poured into 1 L of 5% HCl, and the product was extracted with CH_2Cl_2 (3×150 mL). The extract was washed with water to neutral reaction, and dried with $MgSO_4$, the solvent was evaporated, and the residue was fractionated *in vacuo* to give 42.5 g (80%) of acrylate **1**, b.p. 72—75 °C(15 Torr) [*cf.*, Ref. 1: b.p. 59—62 °C (10 Torr)].

Table 2. Properties and data of elemental analyses for compounds **2**—**8** and **10**

Compound	B.p./°C (*p*/Torr) [m.p./°C]	Found (%) / Calculated C	H	F	S	Molecular formula
2	—	41.4 / 40.8	4.91 / 5.04	31.29 / 30.73	—	$C_{12}H_{17}F_6NO_4$
3	100—102 (4)	35.0 / 35.1	3.35 / 3.51	—	9.28 / 9.35	$C_{10}H_{12}F_6O_4S$
4	110—112 (3)	45.7 / 46.2	4.03 / 4.10	—	7.87 / 8.20	$C_{15}H_{16}F_6O_3S$
5	100—102 (8)	41.8 / 42.2	5.42 / 5.32	—	8.92 / 8.64	$C_{13}H_{20}F_6O_3S$
6	105—108 (9)	44.4 / 44.7	3.68 / 3.72	—	8.32 / 8.51	$C_{14}H_{14}F_6O_3S$
7	85—86 (130)	31.8 / 32.0	3.31 / 3.33	—	10.35 / 10.60	$C_8H_{10}F_6O_3S$
8	[97—99]	19.3 / 19.7	1.28 / 1.36	30.68 / 31.15	—	$C_6H_5F_6IO_3$
10	70—75 (15)	18.3 / 17.9	0.81 / 0.74	28.71 / 28.29	—	$C_6H_3F_6Cl_2IO$

Ethyl 4,4,4-trifluoro-3-hydroxy-2-morpholinomethyl-3-trifluoromethylbutyrate (2). A solution of morpholine (0.36 g, 0.041 mol) in C_6H_6 (3 mL) was added to a solution of acrylate **1** (1.1 g, 0.041 mol) in C_6H_6 (5 mL) with stirring and cooling by ice water. The mixture was stirred for 5 h at 0—5 °C and filtered. The filtrate was concentrated to afford 1.45 g (~100%) of the ester of amino acid **2** as a transparent syrupy liquid.

Ethyl 2-acetylthiomethyl-4,4,4-trifluoro-3-hydroxy-3-trifluoromethylbutyrate (3). A mixture of acrylate **1** (8.9 g, 0.033 mol) and thioacetic acid (5.0 g, 0.065 mol) was heated at 100 °C for 1.5 h. The excess thiocetic acid was distilled off and the residue was fractionated at 4 Torr to yield 9.1 g (80%) of compound **3**.

Ethyl 2-benzylthiomethyl-4,4,4-trifluoro-3-hydroxy-3-trifluoromethylbutyrate (4). A mixture of acrylate **1** (1.33 g, 5 mmol) and α-toluenethiol (0.93 g, 5.5 mmol) was heated at 120 °C for 20 h and then fractionated to afford 1.35 g (70%) of sulfide **4**.

Ethyl 4,4,4-trifluoro-3-hydroxy-2-(*n*-pentylthiomethyl)-3-trifluoromethylbutyrate (5). A mixture of acrylate **1** (1.33 g, 5 mmol), *n*-pentanethiol (0.78 g, 7.5 mmol), and TfOH (0.075 g, 0.5 mmol) was heated at 100—105 °C for 7 h. The reaction mixture was then cooled, treated with saturated aqueous $NaHCO_3$ (5 mL), and extracted with ether (3×20 mL). The extract was dried with $MgSO_4$, the solvent was evaporated, and the residue was fractionated to give 1.38 g (75%) of sulfide **5**.

Ethyl 4,4,4-trifluoro-3-hydroxy-2-phenylthiomethyl-3-trifluoromethylbutyrate (6). A mixture of acrylate **1** (1.6 g, 6 mmol), thiophenol (0.77 g, 7 mmol), and TfOH (0.1 g, 0.6 mmol) was heated at 120 °C for 8 h. The reaction mixture was then cooled and treated with saturated aqueous $NaHCO_3$ (5 mL). The reaction product was extracted with ether (3×20 mL), the extract was dried with $MgSO_4$, the solvent was evaporated, and the residue was fractionated to give 1.75 g (90%) of sulfide **6**.

Reaction of acrylate 1 with α-toluenethiol in the presence of TfOH. A mixture of acrylate **1** (1.33 g, 5 mmol), α-toluenethiol (0.93 g, 7.5 mmol), and TfOH (0.075 g, 0.5 mmol) was heated for 2 h at 50 °C and for 1 h at 80 °C and then cooled. The ^{19}F NMR spectrum contains four signals, two of which are typical of sulfide **4** and the other two of thiol **7** (see Table 1) in 1 : 1.5 ratio.

Ethyl 4,4,4-trifluoro-3-hydroxy-2-mercaptomethyl-3-trifluoromethylbutyrate (7). A mixture of the acetyl derivative **3** (1.1 g, 3.2 mmol) and 15% methanolic HCl (15 mL) was kept at 20 °C for 20 h. The solvent and HCl were distilled at ambient pressure and the residue was fractionated *in vacuo* to give 0.85 g (88%) of thiol **7**.

4,4,4-Trifluoro-3-hydroxy-2-iodomethyl-3-trifluoromethylbutyric acid (8). A solution of acrylate **1** (20.0 g, 0.075 mol) and Me_3SiI (30.0 g, 0.15 mol) in $CHCl_3$ (25 mL) was heated in a sealed tube at 100 °C for 10 h. The reaction mixture was then cooled, the volatile products were distilled off at 40—50 Torr, and the residue was refluxed in MeOH (30 mL) for 1.5 h and concentrated. The residue was washed with saturated aqueous $Na_2S_2O_3$ until complete elimination of traces of I_2 and dissolved in aqueous $NaHCO_3$. The organic layer was removed, and the aqueous solution was acidified with 10% HCl until complete precipitation of the reaction product. The product was extracted with ether (5×40 mL), the ethereal solution was dried with Na_2SO_4, and the ether was removed to give 17.9 g (65%) of crystalline acid **8**.

4,4,4-Trifluoro-3-hydroxy-2-iodomethyl-3-trifluoromethylbutyroyl chloride (9) and 3-chloro-4,4,4-trifluoro-2-iodomethyl-3-trifluoromethylbutyroyl chloride (10). A mixture of acid **8** (18.3 g, 0.05 mol) and $SOCl_2$ (11.9 g, 0.1 mol) was refluxed for 9 h. The excess $SOCl_2$ was distilled off and the residue was fractionated *in vacuo* to give 6.9 g of the product, b.p. 72—75 °C (15 Torr). The ^1H and ^{19}F NMR spectra (in $CDCl_3$) showed the presence of two compounds in a 1 : 1 ratio. Acyl chloride **9**. ^1H NMR, δ: 3.9 (m, 2 H, CH_2); 4.6 (m, 1 H, CH); 8.3 (s, 1 H, OH). ^{19}F NMR, δ: −1.7 (q, 3 F, CF_3); −6.6 (q, 3 F, CF_3). Acyl chloride **10**. The ^1H and ^{19}F NMR spectra are given in Table 1.

3-Chloro-4,4,4-trifluoro-2-iodomethyl-3-trifluoromethylbutyroyl chloride (10). A mixture of acid **8** (4.5 g, 0.0123 mol) and $(COCl)_2$ (4.8 g, 0.0378 mol) was refluxed for 5 h. The excess oxalyl chloride was distilled off, and the residue was fractinated *in vacuo* to give 2.15 g (43%) of acyl chloride **10**.

This study was financially supported by the Russian Foundation for Basic Research (Project No. 96-03-32884).

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Received December 6, 1996