Synthesis and Properties of α-Bromomethyl-Substituted β-Ethoxyvinyl Polyfluoroalkyl Ketones

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Abstract: An efficient and practical method for the synthesis of α-bromomethyl-substituted β-alkoxyvinyl polyfluoroalkyl ketones is reported. These highly functionalized α-bromomethyl enones easily react with various nucleophiles and binucleophiles affording a wide variety of new functionalized enones and heterocyclic systems that are perspective starting materials for the synthesis of compounds with potentially high biological and pharmacological activity.

Key words: enones, fluorine, halogenation, radical reaction, nucleophilic reaction, heterocycles

The introduction of fluorine atoms and fluorinated groups into organic molecules often confers significant and useful changes to their chemical and physical properties[1] that are actively used by medicinal and agricultural chemists. As a result, the occurrence of fluorine-substituted compounds in new commercial pharmaceutical substances has increased from 2% in 1970 to about 20% today. The market share of fluoro-containing compounds as new agrochemicals is higher, above 28%.[2] Methods for the synthesis of fluorinated compounds have received considerable interest in recent years.[3] Although direct fluorinating or polyfluoroalkylating methods are the most attractive and powerful new tools for constructing fluorinated compounds,[4] fluoro-containing building blocks are often more convenient starting reagents.[5] Fluorinated carbonyl and dicarbonyl compounds are often used as starting materials to obtain the desired fluoro-containing substances.[6] Particularly, (*E*)-β-alkoxyvinyl polyfluoroalkyl ketones **1** are versatile polyfluoroalkylated building blocks for the synthesis of various fluoro-containing heterocycles, enaminones, dyes, drugs, and protective reagents for amino group protection in peptide synthesis.[7] Enones **1** may be considered as synthetic equivalents of 1,3-ketoaldehydes or 1,3-diketones, and they are readily available by the reaction of polyfluoroacylation reagents with alkyl vinyl ethers (Figure 1). Whereas the nucleophilic reactions of enones **1** have been studied in detail,[8] there only a few reports on the reactions of fluorinated enones **1** with electrophiles such as halogens.[9]

Earlier we showed that the structure of starting fluorinated enones **1** plays a key role in the pathway of the bromination reaction (Scheme 1).[9a] The bromination of compounds **1a** gives α-bromo-substituted enones **2** by an addition–dehydrohalogenation mechanism.[9a] It is a good starting material for numerous heterocyclic syntheses.[9b,10] The products of allylic bromination, compounds **3**, were formed by the reaction of **1b** with bromine. Brominated enones **2** and **3** can be easily transformed into various fluorinated heterocycles, phosphonates, phosphates, etc.[11] Also the complex behavior of cyclic and linear fluorinated 1,3-dicarbonyls and their boron and metal derivatives towards such halogenating agents as bromine, *N*-bromosuccinimide, and sulfuryl chloride was recently studied and products with various structures were characterized.[5c]

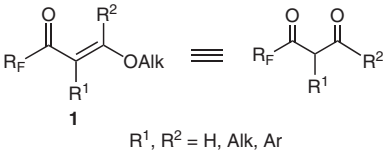
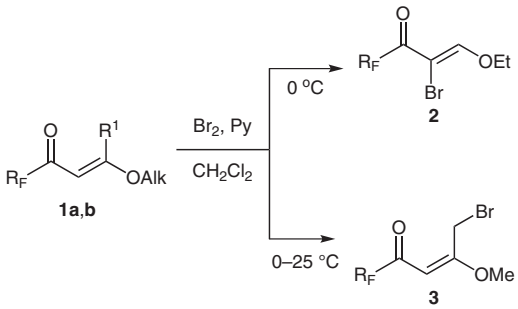


Figure 1 Enones **1** as synthetic equivalent of 1,3-ketoaldehydes or 1,3-diketones



Scheme 1 Reactions of enones **1** with bromine

At that time, the bromination of α-methyl-substituted enones had not been reported. Taking into account the interest in halogen-substituted fluoro-containing enones, we have now developed a simple and effective synthesis of α-bromomethyl-containing fluorinated enones. The synthetic potential of this class of compounds has been investigated for the example of a trifluoromethyl-containing enone.

A series of α-methyl-substituted enones **4a**–**e** was synthesized by the reaction of an *E*,*Z*-mixture of 1-ethoxyprop-1-ene with the corresponding acyl chloride or anhydride

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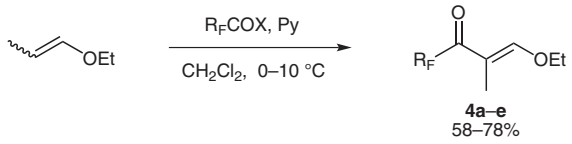
in high yields by a general method (Scheme 2).[5i,12] The structure of obtained enones **4a**–**e** was confirmed by ^{1}H, ^{19}F, and ^{13}C NMR analysis.



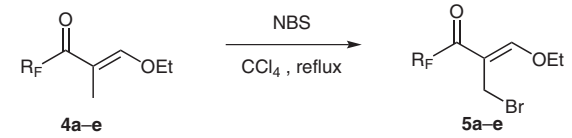
R_F = CF_3 (**a**), C_2F_5 (**b**), C_3F_7 (**c**), CF_2H (**d**), CF_2Cl (**e**)
X = $OC(O)CF_3$ (**a**), Cl (**b**–**e**)

Scheme 2 Synthesis of enones **4a**–**e**

First, we checked the reaction of enone **4a** with bromine and observed neither the addition of bromine to the carbon–carbon double bond nor the bromination of the methyl group in compound **4a** in a reaction mixture containing an excess of bromine in dichloromethane or deuterochloroform at room temperature. This was clearly proved by ^{1}H and ^{19}F NMR spectroscopy: only a small shift in the signals of the trifluoromethyl and methyl groups and the olefinic proton was observed. Moreover, after workup we recovered 80–90% of enone **4a**.

It was found that compounds **4a**–**e** readily react with *N*-bromosuccinimide in boiling tetrachloromethane in the presence of benzoyl peroxide, and α-bromomethyl-substituted enones **5a**–**e** were formed in high yields (Table 1). All obtained compounds were purified by vacuum distillation and fully characterized by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy and elemental analysis. It is worth to mention that enones **5a**–**e** possess *Z*-configuration (*trans*-position of alkoxy and acyl groups), a property being characteristic for β-alkoxyvinyl polyfluoroalkyl ketones.[12a]

Table 1 Synthesis of **5a**–**e**

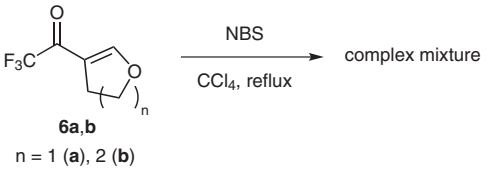


R_F = CF_3 (**a**), C_2F_5 (**b**), C_3F_7 (c), CF_2H (**d**), CF_2Cl (**e**)

R_F	Starting compound	Product	Bp (°C/Torr)	Yield[a] (%)
CF_3	**4a**	**5a**	115–118/10	70
C_2F_5	**4b**	**5b**	120–125/10	69
C_3F_7	**4c**	**5c**	130–135/10	69
CF_2H	**4d**	**5d**	131–134/10	64
CF_2Cl	**4e**	**5e**	128–132/10	71

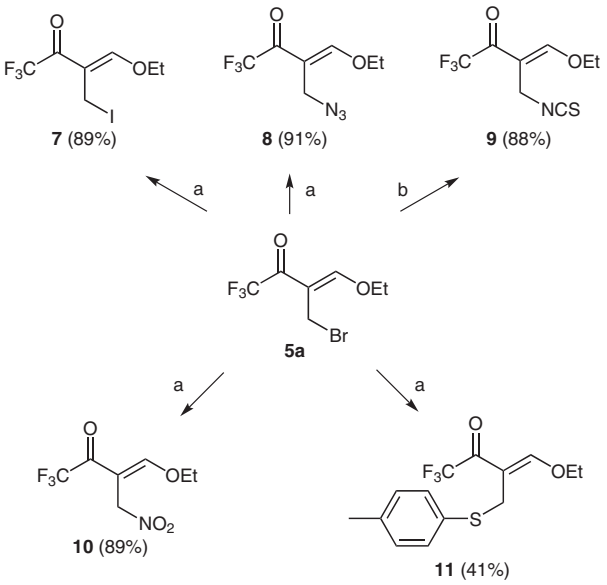
[a] Yield of isolated product.

It should be noted that *N*-chlorosuccinimide did not react with enone **4a** under the same conditions (boiling CCl_4, benzoyl peroxide). Structural analogues of **4a**, cyclic enones **6a**,**b**, reacted with *N*-bromosuccinimide to form complex mixtures of products (Scheme 3).



Scheme 3 Reaction of **6a**,**b** and *N*-bromosuccinimide

Synthesized enones **5** are highly functionalized substances that have several potential reactive centers in their structure for nucleophilic attack: carbon atoms in the carbonyl group, at the β-position of the carbon–carbon double bond, and at the bromomethyl group. We used trifluoromethyl-containing enone **5a** as a model compound to investigate reactions of enones **5** with nucleophiles of various natures. We found that **5a** readily reacts with typical nucleophiles: sodium iodide, sodium azide, potassium thiocyanate, sodium nitrite, 4-methylbenzenethiol, and the corresponding products **7**–**11** were formed in 41–91% yields (Scheme 4).

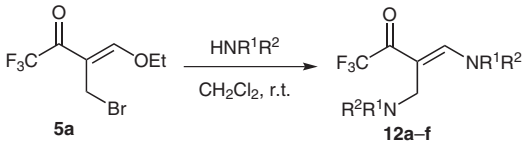


Scheme 4 Reactions of **5a** with nucleophiles. *Reagents and conditions*: (a) corresponding nucleophilic reagent (NaN_3, KSCN, NaI, or $NaNO_2$), acetone, r.t.; (b) 4-methylbenzenethiol, K_2CO_3, acetone, r.t.

It is worthy to note that the reaction of the **5a** with the ambident nucleophile sodium thiocyanate led to isothiocyanate **9**, in contrast to previously published results for β-bromomethyl trichloromethyl enone that gave the corresponding thiocyanate.[13] The proposed isothiocyanate group containing structure of compound **9** is based on the analysis of ^{13}C NMR spectroscopic data: the characteristic signal of the isothiocyanate function at δ =133.3 was observed, and, moreover, the characteristic absorption band for the isothiocyanate group at 2061 cm^{-1} (N=C=S) is present in the IR spectra.

Earlier it was shown that enones **1** react with aliphatic amines under mild conditions leading to the corresponding enaminones.[9a,14] We found that the addition of one equivalent of a secondary aliphatic amine to a solution of enone **5a** leads to a complex unidentifiable mixture of products. However we could synthesize and fully characterize by NMR spectroscopy the products **12a–f** from the reaction of one molecule of enone **5a** and two molecules of amine by changing the order of the addition of the reagents and using a large excess of amine (Table 2).

Table 2 Reaction of **5a** with Secondary Amines

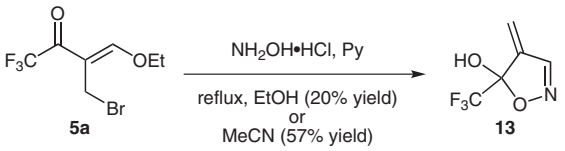


Amine	Product	Mp[a] (°C)	Yield[b] (%)
Me_2NH	**12a**	wax	40
Et_2NH	**12b**	oil	65
i-Pr_2NH	**12c**	oil	50
pyrrolidine	**12d**	78–79	48
piperidine	**12e**	87–89	46
morpholine	**12f**	93–95	79

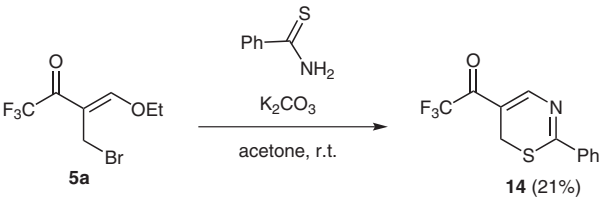
[a] From hexane.
[b] Yield of isolated product.

Enones **5** are promising compounds as starting materials for heterocyclization reactions with binucleophiles, but all our attempts to involve enone **5a** in reactions with hydrazine hydrate, amidines, urea, and thiourea led to the formation of complex mixtures of unidentified products under various reaction conditions (solvent: EtOH, CH_2Cl_2, AcOH; base: pyridine, K_2CO_3; r.t. and boiling EtOH). Unfortunately, these mixtures could not be separated by column chromatography to yield pure compounds. We suppose the formation of the mixtures of products occurs as a result of unselective reaction of various reactive centers in enone **5a** and the above-mentioned binucleophiles. Apart from these negative results, the reaction between enone **5a** and hydroxylamine in boiling ethanol led to the formation of an unexpected five-membered heterocyclic compound **13** in 20% yield (Scheme 5). The replacement of ethanol by acetonitrile increased the yield of compound **13** up to 57%. The heterocycle **13** was purified by column chromatography and fully characterized by ^1H, ^{19}F, and ^{13}C NMR spectroscopy and mass spectrometry.

The reaction of **5a** with thiobenzamide gave 2-phenyl-5-trifluoroacetyl-6*H*-1,3-thiazine (**14**) in 21% yield (Scheme 6). The structure of **14** was proved by ^1H, ^{19}F, and ^{13}C NMR spectroscopy and confirmed by X-ray crystal structure analysis (Figure 2). Compound **14** is of interest as a possible starting material for the synthesis of new trifluoromethyl-containing cephem analogues.[15]



Scheme 5 Reaction of **5a** with hydroxylamine



Scheme 6 Synthesis of **14**

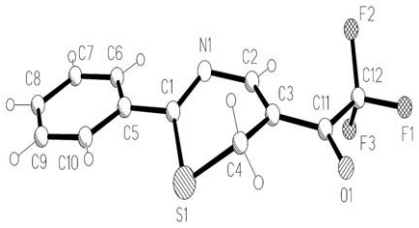


Figure 2 Single crystal X-ray structure of **14**[16]

In conclusion, we have studied the bromination reaction of α-methyl-substituted trifluoroacetyl-containing enones with elemental bromine and *N*-bromosuccinimide. The method allows new polyfunctional α-bromomethyl-containing fluorinated enones **5** to be obtained in preparative quantities. Using trifluoromethyl-containing enone **5a**, the reactivity of this class of compounds with various nucleophiles and binucleophiles was investigated. Similarities and differences of chemical properties between enones **5** and previously published β-bromomethyl-containing analogues were shown. New perspective synthons for the synthesis of polyfluoroalkylated, potentially bioactive, heterocycles, trifluoromethyl-bearing dihydroisoxazolinol **13** and trifluoroacetyl-containing 6*H*-1,3-thiazine **14**, were synthesized and characterized.

Solvents were purified according to standard procedures. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance DRX 500 (500 MHz) and Varian Unity plus 400 (400 MHz) spectrometers referenced to TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. IR spectra were recorded on Bruker Vertex 70. Agilent 1200 Series LC/MSD system with DAD\ELSD and Agilent LC\MSD SL (G6130A), SL (G6140A) mass spectrometer, all the LC/MS data were obtained using positive/negative mode switching. The progress of reactions was monitored by TLC (silica gel 60 F254, Merck). Column chromatography was carried out on silica gel 60 (Merck No. 109385, particle size 0.040–0.063). All starting materials were of the highest commercial quality and were used without further purification. The synthesis of starting enones **4** was recently published.[5i]

α-Bromomethyl Enones 5a–e; General Procedure
A solution of α-methyl enone **4** (100 mmol), NBS (35.6 g, 200 mmol), and $(BzO)_2$ (2.4 g, 10 mmol) in anhydrous CCl_4 (300 mL) was stirred at reflux for 2 h. The end of the reaction was determined by TLC (EtOAc–hexane, 1:4). The cold mixture was filtered, and the solvent was removed under vacuum. The residue was distilled under vacuum to give α-bromomethyl enones with 90–95% purity as white or yellow low-melting crystals or an oil.

(*Z*)-3-(Bromomethyl)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (5a)
White low-melting crystals; yield: 18.3 g (70%); bp 115–118 °C/10–12 Torr.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.22 (s, 2 H), 1.45 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.8 (q, *J* = 35.0 Hz), 166.7 (q, *J* = 4.5 Hz), 116.7 (q, *J* = 290.7 Hz), 113.9, 73.5, 20.7, 15.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.40 (s).

Anal. Calcd for $C_7H_8BrF_3O_2$: C, 32.21; H, 3.09. Found: C, 32.34; H, 3.20.

(*Z*)-2-(Bromomethyl)-1-ethoxy-4,4,5,5,5-pentafluoropent-1-en-3-one (5b)
Yellow low-melting crystals; yield: 21.5 g (69%); bp 120–125 °C/10–12 Torr.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (s, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.21 (s, 2 H), 1.44 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 179.9 (t, *J* = 26.0 Hz), 167.2 (t, *J* = 8.6 Hz), 118.0 (qt, *J* = 286.6, 34.3 Hz), 115.6, 108.8 (tq, *J* = 267.8, 37.1 Hz), 76.6, 20.8, 15.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –82.36 (br s, 3 F), –114.86 (br s, 2 F).

Anal. Calcd for $C_8H_8BrF_5O_2$: C, 30.89; H, 2.59. Found: C, 30.98; H, 2.64.

(*Z*)-2-(Bromomethyl)-1-ethoxy-4,4,5,5,6,6,6-heptafluorohex-1-en-3-one (5c)
Yellow low-melting crystals; yield: 25.0 g (69%); bp 130–135 °C/10–12 Torr.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 4.22 (s, 2 H), 1.44 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 179.5 (t, *J* = 25.4 Hz), 167.3 (t, *J* = 9.1 Hz), 121.3–106.0 (m), 116.4, 73.6, 21.0, 15.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.70 (t, *J* = 9.1 Hz, 3 F), –113.25 (q, *J* = 9.1 Hz, 2 F), –126.35 (br s, 2 F).

Anal. Calcd for $C_9H_8BrF_7O_2$: C, 29.94; H, 2.23. Found: C, 30.03; H, 2.34.

(*Z*)-3-(Bromomethyl)-4-ethoxy-1,1-difluorobut-3-en-2-one (5d)
Yellow oil; yield: 15.6 g (64%); bp 131–134 °C/10–12 Torr.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (s, 1 H), 5.99 (t, *J* = 53.9 Hz, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 4.20 (s, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 185.3 (t, *J* = 25.7 Hz), 166.0 (t, *J* = 6.1 Hz), 114.6, 112.0 (t, *J* = 254.7 Hz), 73.0, 21.1, 15.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –119.95 (d, *J* = 53.8 Hz).

Anal. Calcd for $C_7H_9BrF_2O_2$: C, 34.59; H, 3.73. Found: C, 34.63; H, 3.64.

(*Z*)-3-(Bromomethyl)-1-chloro-4-ethoxy-1,1-difluorobut-3-en-2-one (5e)
Yellow low-melting crystals; yield: 19.7 g (71%); bp 128–132 °C/10–12 Torr.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (s, 1 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 4.23 (s, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 179.0 (t, *J* = 29.0 Hz), 166.6 (t, *J* = 6.0 Hz), 120.4 (t, *J* = 304.1 Hz), 112.4, 73.4, 21.5, 15.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –59.23 (s).

Anal. Calcd for $C_7H_8BrClF_2O_2$: C, 30.30; H, 2.91. Found: C, 30.18; H, 2.73.

Reaction of α-Bromomethyl Enone 5a with Nucleophiles To Give Compounds 7–10; General Procedure
A solution of **5a** (2.61 g, 10 mmol) and the corresponding nucleophilic reagent (NaI, NaN_3, KSCN, or $NaNO_2$) (30 mmol) in acetone (20 mL) was stirred at r.t. for 12 h. The end of the reaction was determined by TLC (EtOAc–hexane, 1:4). The mixture was filtered and the solvent was removed under vacuum. The residue was a crude product with high purity (93–96% by NMR spectroscopy data).

(*Z*)-4-Ethoxy-1,1,1-trifluoro-3-(iodomethyl)but-3-en-2-one (7)
Pale yellow oil; yield: 2.75 g (89%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (s, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.09 (s, 2 H), 1.47 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.5 (q, *J* = 35.0 Hz), 165.6–165.4 (br m), 116.8 (q, *J* = 290.7 Hz), 115.2, 73.4, 15.6, –8.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.22 (s).

Anal. Calcd for $C_7H_8F_3IO_2$: C, 27.29; H, 2.62. Found: C, 27.12; H, 2.43.

(*E*)-3-(Azidomethyl)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (8)
Pale yellow oil; yield: 2.04 g (91%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 4.08 (s, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.9 (q, *J* = 34.8 Hz), 167.4 (q, *J* = 4.4 Hz), 116.8 (q, *J* = 290.9 Hz), 111.3, 73.3, 42.7, 15.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.36 (s).

Anal. Calcd for $C_7H_8F_3N_3O_2$: C, 37.68; H, 3.61; N, 18.83. Found: C, 37.73; H, 3.51; N, 18.96.

(*E*)-4-Ethoxy-1,1,1-trifluoro-3-(isothiocyanatomethyl)but-3-en-2-one (9)
Pale yellow oil; yield: 2.10 g (88%).

IR (CCl_4): 1695 (C=O), 2061 cm^{-1} (N=C=S).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 4.40–4.27 (m, 4 H), 1.46 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.0 (q, *J* = 35.1 Hz), 167.2 (q, *J* = 4.5 Hz), 133.3, 116.7 (q, *J* = 290.9 Hz), 110.5, 73.7, 37.4, 15.4.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –70.43 (s).

Anal. Calcd for $C_8H_8F_3NO_2S$: C, 40.17; H, 3.37; N, 5.86. Found: C, 40.29; H, 3.21; N, 5.67.

(*E*)-4-Ethoxy-1,1,1-trifluoro-3-(nitromethyl)but-3-en-2-one (10)
Pale yellow oil; yield: 2.03 g (89%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87 (s, 1 H), 5.24 (s, 2 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 1.44 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.2 (q, *J* = 35.6 Hz), 168.8 (d, *J* = 4.2 Hz), 116.7 (q, *J* = 290.1 Hz), 107.1, 74.0, 67.1, 15.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.77 (s).

Anal. Calcd for $C_7H_8F_3NO_4$: C, 37.02; H, 3.55; N, 6.17. Found: C, 37.13; H, 3.51; N, 6.06.

(*Z*)-4-Ethoxy-1,1,1-trifluoro-3-[(*p*-tolylthio)methyl]but-3-en-2-one (11)
To a stirred solution of **5a** (0.50 g, 1.92 mmol) and 4-methylbenzenethiol (0.24 g, 1.92 mmol) in acetone (20 mL), K_2CO_3 (0.29 g, 2.11 mmol) was added. The mixture was stirred at r.t. for 4 h to complete

the reaction. The end of the reaction was determined by TLC (EtOAc–hexane, 2:1). The mixture was filtered, the solvent was removed under vacuum and the residue was purified by column chromatography (EtOAc–hexane, 2:1). The product **11** (0.24 g, 41%) was obtained as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (s, 1 H), 7.34 (d, *J* = 7.9 Hz, 2 H), 7.08 (d, *J* = 7.9 Hz, 2 H), 4.04 (q, *J* = 7.1 Hz, 2 H), 3.77 (s, 2 H), 2.31 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.6 (q, *J* = 34.3 Hz), 164.0 (q, *J* = 4.3 Hz), 137.4, 132.0, 132.1, 129.5, 116.9 (q, *J* = 291.3 Hz), 114.1, 72.3, 28.5, 21.2, 15.1.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –69.82 (s).

Anal. Calcd for $C_{14}H_{15}F_3O_2S$: C, 55.25; H, 4.97. Found: C, 55.44; H, 5.08.

α-Aminomethyl Enaminones 12a–f; General Procedure

A solution of **5a** (1.3 g, 5 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of the respective secondary amine (25 mmol) in CH_2Cl_2 (30 mL) under stirring. The mixture was stirred at r.t. for 1 h. The mixture was filtered, and the organic phase was washed with H_2O and dried (Na_2SO_4). After evaporation of the solvent, the residue was crystallized (if necessary) from hexane to afford pure products.

(*E*)-4-(Dimethylamino)-3-[(dimethylamino)methyl]-1,1,1-trifluorobut-3-en-2-one (12a)

Grey-brown wax; yield: 0.44 g (40%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (s, 1 H), 3.23 (s, 6 H), 3.08 (s, 2 H), 2.06 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.4 (q, *J* = 29.9 Hz), 156.8, 118.6 (q, *J* = 292.6 Hz), 101.5, 51.1, 43.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –66.25 (s).

Anal. Calcd for $C_9H_{15}F_3N_2O$: C, 48.21; H, 6.74; N, 12.49. Found: C, 48.35; H, 6.88; N, 12.40.

(*E*)-4-(Diethylamino)-3-[(diethylamino)methyl]-1,1,1-trifluorobut-3-en-2-one (12b)

Brown oil; yield: 0.91 g (65%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (s, 1 H), 3.62 (br m, 4 H), 3.31 (s, 2 H), 2.46 (q, *J* = 7.1 Hz, 4 H), 1.26 (t, *J* = 7.1 Hz, 6 H), 0.97 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.9 (q, *J* = 29.8 Hz), 155.0 (q, *J* = 4.3 Hz), 118.8 (q, *J* = 292.6 Hz), 101.3, 46.9, 45.1, 14.9, 11.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.73 (s).

Anal. Calcd for $C_{13}H_{23}F_3N_2O$: C, 55.70; H, 8.27; N, 9.99. Found: C, 55.56; H, 8.13; N, 10.15.

(*E*)-4-(Diisopropylamino)-3-[(diisopropylamino)methyl]-1,1,1-trifluorobut-3-en-2-one (12c)

Brown oil; yield: 0.84 g (50%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (s, 1 H), 5.47 (br s, 1 H), 3.67 (br s, 1 H), 3.47 (s, 2 H), 3.00 (br s, 2 H), 1.23 (br s, 12 H), 1.00 (br s, 12 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.1 (q, *J* = 28.5 Hz), 151.4, 119.1 (q, *J* = 293.6 Hz), 101.0, 50.2, 47.8, 46.3, 20.7, 20.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.22 (s).

Anal. Calcd for $C_{17}H_{31}F_3N_2O$: C, 60.69; H, 9.29; N, 8.33. Found: C, 60.90; H, 9.31; N, 8.42.

(*E*)-1,1,1-Trifluoro-4-(pyrrolidin-1-yl)-3-(pyrrolidin-1-ylmethyl)but-3-en-2-one (12d)

White solid; yield: 0.66 g (48%), mp 78–79 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (s, 1 H), 3.93 (br s, 2 H), 3.63 (br m, 2 H), 3.35 (s, 2 H), 2.45 (br m, 4 H), 1.95 (br m, 4 H), 1.68 (br m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.1 (q, *J* = 30.2 Hz), 152.8, 118.8 (q, *J* = 292.6 Hz), 103.0, 52.0, 47.8, 23.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –66.06 (s).

Anal. Calcd for $C_{13}H_{19}F_3N_2O$: C, 56.51; H, 6.93; N, 10.14. Found: C, 56.47; H, 6.75; N, 10.26.

(*E*)-1,1,1-Trifluoro-4-(piperidin-1-yl)-3-(piperidin-1-ylmethyl)but-3-en-2-one (12e)

White solid; yield: 0.70 g (46%); mp 87–89 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (s, 1 H), 3.67 (br s, 4 H), 3.17 (s, 2 H), 2.29 (br m, 4 H), 1.68 (br m, 6 H), 1.45 (br m, 4 H), 1.38 (br m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.9 (q, *J* = 30.2 Hz), 154.0, 118.8 (q, *J* = 292.5 Hz), 100.3, 53.1, 51.7, 26.0, 26.4, 24.7, 24.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.88 (s).

Anal. Calcd for $C_{15}H_{23}F_3N_2O$: C, 59.20; H, 7.62; N, 9.20. Found: C, 59.35; H, 7.54; N, 9.39.

(*E*)-1,1,1-Trifluoro-4-morpholino-3-(morpholinomethyl)but-3-en-2-one (12f)

Grey solid; yield: 1.21 g (79%); mp 93–95 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (s, 1 H), 3.76 (br m, 8 H), 3.58 (br m, 4 H), 3.24 (s, 2 H), 2.37 (br m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.2 (q, *J* = 30.4 Hz), 154.0–154.7 (m), 118.4 (q, *J* = 292.8 Hz), 100.0, 67.2, 67.0, 52.2, 51.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –66.48 (s).

Anal. Calcd for $C_{13}H_{19}F_3N_2O_3$: C, 50.65; H, 6.21; N, 9.09. Found: C, 50.78; H, 6.20; N, 9.23.

4-Methylene-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (13)

To a solution of $NH_2OH{\cdot}HCl$ (0.11 g, 1.59 mmol) in MeCN (10 mL) was added pyridine (0.25 g, 3.17 mmol) and **5a** (0.41 g, 1.59 mmol). The mixture was stirred for 10 h at reflux. After cooling, the solvent was evaporated and the residue was column chromatographed (silica gel, EtOAc–hexane, 2:1) to give product **13** (0.15 g, 57%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (s, 1 H), 5.93 (s, 1 H), 5.90 (s, 1 H), 4.56 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.1, 142.8, 121.9, 121.3 (q, *J* = 284.4 Hz), 99.7 (q, *J* = 34.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.57 (s).

MS (CI): *m*/*z* (%) = 168 (100) $[M + 1]^+$.

Anal. Calcd for $C_5H_4F_3NO_2$: C, 35.94; H, 2.41; N, 8.38. Found: C, 36.15; H, 2.54; N, 8.36.

2,2,2-Trifluoro-1-(2-phenyl-6*H*-1,3-thiazin-5-yl)ethanone (14)

A solution of **5a** (1.00 g, 3.93 mmol), benzothioamide (0.53, 3.93 mmol), and K_2CO_3 (0.58 g, 0.42 mmol) in acetone (25 mL) was stirred at r.t. for 4 h. The mixture was filtered, the solvent was removed, and the residue was chromatographed (EtOAc–hexane 1:15) to give product **14** (0.25 g, 21%) as yellow crystals; mp 74–76 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (s, 1 H), 8.10 (d, *J* = 7.7 Hz, 2 H), 7.62 (t, *J* = 6.8 Hz, 1 H), 7.51 (br dd, both *J* ~ 7.0 Hz, 2 H), 3.75 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 179.4 (q, *J* = 35.8 Hz), 172.6, 152.3 (q, *J* = 4.7 Hz), 136.8, 133.8, 129.5, 129.0, 116.7 (q, *J* = 290.6 Hz), 110.3, 21.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.72 (s).

Anal. Calcd for $C_{12}H_8F_3NOS$: C, 53.13; H, 2.97; N, 5.16. Found: C, 53.27; H, 2.79; N, 5.04.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Begue, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, **2008**.

(2) (a) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (b) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(3) Some recent reviews, see (a) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (b) Vorbrüggen, H. *Helv. Chim. Acta* **2011**, *94*, 947. (c) Grygorenko, O. O.; Artamonov, O. S.; Komarov, I. V.; Mikhaylyuk, P. K. *Tetrahedron* **2011**, *67*, 803. (d) Acena, J. L.; Sorochinsky, A. E.; Soloshonok, V. A. *Synthesis* **2012**, *44*, 1591.

(4) For some recent examples, see: (a) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 536. (b) Parsons, A. T.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 9120. (c) Jiang, X.; Chu, L.; Qing, F.-L. *J. Org. Chem.* **2012**, *77*, 1251. (d) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410. (e) Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13588. (f) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Bucholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901. (g) Artamonov, O. S.; Slobodyanyuk, E. Y.; Shishkin, O. V.; Komarov, I. V.; Mikhaylyuk, P. K. *Synthesis* **2013**, *45*, 0225. (h) Fujikawa, K.; Kobayashi, A.; Amii, H. *Synthesis* **2012**, *44*, 3015.

(5) (a) Sevenard, D. V.; Kazakova, O.; Schoth, R.-M.; Lork, E.; Röschenthaler, G.-V. *J. Chem. Crystallogr.* **2011**, *41*, 1795. (b) Loop, I.; Skarpos, H.; Kalinovich, N.; Kazakova, O.; Lork, E.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2010**, *131*, 389. (c) Sevenard, D. V.; Vorobyev, M.; Sosnovskikh, V. Ya.; Wessel, H.; Kazakova, O.; Vogel, V.; Shevchenko, N. E.; Nenajdenko, V. G.; Lork, E.; Röschenthaler, G.-V. *Tetrahedron* **2009**, *65*, 7538. (d) Irgashev, R. A.; Sosnovskikh, V. Ya.; Kalinovich, N.; Kazakova, O.; Röschenthaler, G.-V. *Tetrahedron Lett.* **2009**, *50*, 4903. (e) Sevenard, D. V.; Kazakova, O.; Schoth, R.-M.; Lork, E.; Chizhov, D. L.; Poveleit, J.; Röschenthaler, G.-V. *Synthesis* **2008**, 1867. (f) Sevenard, D. V.; Kazakova, O.; Lork, E.; Duelcks, T.; Chizhov, D. L.; Röschenthaler, G.-V. *J. Mol. Struct.* **2007**, *846*, 87. (g) Tolmachova, N. A.; Dolovanyuk, V. G.; Gerus, I. I.; Kondratov, I. S.; Polovinko, V. V.; Bergander, K.; Haufe, G. *Synthesis* **2011**, 1149. (h) Tolmacheva, N. A.; Gerus, I. I.; Dolovanyuk, V. G.; Kondratov, I. S.; Haufe, G. *Eur. J. Org. Chem.* **2009**, 5012. (i) Kondratov, I. S.; Dolovanyuk, V. G.; Tolmachova, N. A.; Gerus, I. I.; Bergander, K.; Fröhlich, R.; Haufe, G. *Org. Biomol. Chem.* **2012**, *10*, 8778.

(6) (a) Zhu, S. Z.; Wang, Y. L.; Peng, W. M.; Song, L. P.; Jin, G. F. *Curr. Org. Chem.* **2002**, *6*, 1057. (b) Schoth, R. M.; Sevenard, D.; Pashkevich, K.; Röschenthaler, G.-V. *Coord. Chem. Rev.* **2000**, *210*, 101.

(7) Reviews on fluorinated enones and enaminones: (a) Nenajdenko, V. G.; Sanin, A. V.; Balenkova, E. S. *Russ. Chem. Rev.* **1999**, *68*, 483. (b) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. *Tetrahedron* **2007**, *63*, 7753.

(8) Some recent articles, see: (a) Song, T.; Zhao, J.; Jiang, H.; Zhu, S.; Liu, L.; Xu, L. *Tetrahedron* **2012**, *68*, 5677. (b) Chopin, N.; Decamps, S.; Gouger, A.; Medebielle, M.; Picot, S.; Bienvenu, A.-L.; Pilet, G. *J. Fluorine Chem.* **2011**, *132*, 850. (c) Xin, Y.; Zhao, J.; Zhu, S. *J. Fluorine Chem.* **2012**, *133*, 98. (d) Kim, M. S.; Ryu, H.; Kang, D. W.; Cho, S.-H.; Seo, S.; Park, Y. S.; Kim, M.-Y.; Kwak, E. J.; Kim, Y. S.; Bhondwe, R. S.; Kim, H. S.; Lee, J.; Park, S.-G.; Son, K.; Choi, S.; Deandrea-Lazarus, I. A.; Pearce, L. V.; Blumberg, P. M.; Frank, R.; Bahrenberg, G.; Stockhausen, H.; Koegel, B. Y.; Schiene, K.; Christoph, T. *J. Med. Chem.* **2012**, *55*, 8392. (e) Nunes, C. M.; Ramos Silva, M.; Matos Beja, A.; Fausto, R.; Pinho e Melo, T. M. V. D. *Tetrahedron Lett.* **2010**, *51*, 411. (f) Chopin, N.; Medebielle, M.; Pilet, G. *Eur. J. Inorg. Chem.* **2012**, 1093. (g) Baharfar, R.; Azimi, R. *Chin. Chem. Lett.* **2011**, *22*, 1183. (h) Tolmachova, N. A.; Gerus, I. I.; Vdovenko, S. I.; Haufe, G.; Kirzhner, Y. A. *Synthesis* **2007**, 3797.

(9) (a) Gerus, I. I.; Kacharova, L. M.; Vdovenko, S. I. *Synthesis* **2001**, 431. (b) Volle, J.-N.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 1490.

(10) (a) Rulev, A. Yu.; Fedorov, S. V.; Nenajdenko, V. G.; Balenkova, E. S.; Voronkov, M. G. *Russ. Chem. Bull.* **2003**, *52*, 2287. (b) Fedorov, S. V.; Rulev, A. Yu.; Chipanina, N. N.; Shulunova, A. M.; Nenajdenko, V. G.; Balenkova, E. S.; Tyurin, D. A.; Turchaninov, V. K. *Russ. Chem. Bull.* **2005**, *54*, 103. (c) Nenajdenko, V. G.; Reznichenko, A. L.; Balenkova, E. S. *Russ. Chem. Bull.* **2006**, *55*, 172. (d) Kacharova, L. M.; Gerus, I. I.; Kacharov, A. D. *J. Fluorine Chem.* **2002**, *117*, 193.

(11) (a) Shaitanova, E. N.; Gerus, I. I.; Kukhar, V. P. *Tetrahedron Lett.* **2008**, *49*, 1184. (b) Tarasenko, K. V.; Gerus, I. I.; Kukhar, V. P. *J. Fluorine Chem.* **2007**, *128*, 1264. (c) Tarasenko, K. V.; Kukhar, V. P.; Gerus, I. I.; Manoylenko, O. V.; Röschenthaler, G.-V. *Tetrahedron Lett.* **2010**, *51*, 4623. (d) Zanatta, N.; Schneider, J. M. F. M.; Schneider, P. H.; Wouters, A. D.; Bonacorso, H. G.; Martins, M. A. P.; Wessjohann, L. A. *J. Org. Chem.* **2006**, *71*, 6996. (e) Martins, M. A. P.; Sinhorin, A. P.; Rosa, A.; Flores, A. F. C.; Wastowski, A. D.; Pereira, C. M. P.; Flores, D. C.; Beck, P.; Freitag, R. A.; Brondani, S.; Cunico, W.; Bonacorso, H. G.; Zanatta, N. *Synthesis* **2002**, 2353. (f) Tarasenko, K. V.; Gerus, I. I.; Kukhar, V. P.; Polovinko, V. V. *Collect. Czech. Chem. Commun.* **2009**, *74*, 335. (g) Zanatta, N.; Flores, D. C.; Madruga, C. C.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2006**, *47*, 573. (h) Zanatta, N.; Flores, D. C.; Amaral, S. S.; Bonacorso, H. G.; Martins, M. A. P.; Flores, A. F. C. *Synlett* **2005**, 3079.

(12) (a) Hojo, M.; Masuda, R.; Okada, E.; Sakaguchi, S.; Narumiya, H.; Morimoto, K. *Tetrahedron Lett.* **1989**, *30*, 6173. (b) Mamat, C.; Pundt, T.; Schmidt, A.; Langer, P. *Tetrahedron Lett.* **2006**, *47*, 2183. (c) Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, 483. (d) Bravo, P.; Bruche, L.; Farina, A.; Gerus, I. I.; Kolytcheva, M. T.; Kukhar, V. P.; Meille, S. V.; Viani, F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1667.

(13) Martins, M. A. P.; Sinhorin, A. P.; Zimmermann, N. E. K.; Zanatta, N.; Bonacorso, H. G.; Bastos, G. P. *Synthesis* **2001**, 1959.

(14) (a) Gorbunova, M. G.; Gerus, I. I.; Galushko, S. V.; Kukhar, V. P. *Synthesis* **1991**, 207. (b) Buback, M.; Tost, W.; Hübsch, T.; Voss, E.; Tietze, L. F. *Chem. Ber.* **1989**, *122*, 1179. (c) Sanin, A. V.; Nenajdenko, V. G.; Smolko, K. I.;

Denisenko, D. I.; Balenkova, E. S. *Synthesis* **1998**, 842. (d) Gerus, I. I.; Gorbunova, M. G.; Vdovenko, S. I.; Yagupol'skii, Yu. L.; Kukhar, V. P. *Zh. Org. Khim.* **1990**, *26*, 1877. (e) Okada, E.; Masuda, R.; Hojo, M.; Inoue, R. *Synthesis* **1992**, 533.

(15) (a) Pradère, J.-P.; Roze, J. C.; Quinion, H.; Danion-Bougot, R.; Danion, D.; Toupet, L. *Can. J. Chem.* **1986**, *64*, 597. (b) Tuloup, R.; Danion-Bougot, R.; Danion, D.; Pradère, J.-P.; Toupet, L. *Can. J. Chem.* **1989**, *67*, 1125.

(16) Crystallographic data for compound **14** have been deposited with the accession number CCDC 932863 and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.