Synthesis and Properties of β-Ethoxyvinyl Polyfluoroalkyl Ketones

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Abstract: A number of β -ethoxyvinyl polyfluoroalkyl ketones were synthesized by acylation of ethyl vinyl ether with acid chlorides containing polyfluoroalkyl groups of different composition and structure. Some typical nucleophilic reactions of the title compounds with amines were carried out. Two new fluoro-containing pyrimidinoles were synthesized by the reaction of β -ethoxyvinyl polyfluoroalkyl ketones with urea.

Key words: acylations, fluorinated building blocks, enones, enaminones, aminations

The introduction of fluorine atoms and fluorinated groups into organic molecules often confers significant and useful changes in their chemical and physical properties. Therefore, methods for the synthesis of fluorinated compounds have received considerable interest in recent years.¹ Though direct fluorinating or polyfluoroalkylating methods are the most attractive and powerful new tools for constructing fluorinated compounds, the fluoro-containing building blocks are the more convenient starting reagents.² Thus, fluorinated carbonyl and dicarbonyl compounds are often used as starting materials to obtain the desired fluoro-containing substances. Particularly (E)-4ethoxy-1,1,1-trifluorobut-3-en-2-one (1) (which may be considered as a synthetic equivalent of trifluoroacetylacetaldehyde) is an accessible trifluoromethylated building block for the synthesis of various fluorine-containing dyes, heterocycles, enaminones, drugs, and as a protective reagent for amino group protection in peptide synthesis.³

The most convenient and accessible method for the synthesis of β -ethoxyvinyl trifluoromethyl ketone **1** is the reaction of ethyl vinyl ether with trifluoroacetic anhydride in the presence of pyridine.⁴ For more effective utilization of the fluorinated reagent, we investigated the reaction of polyfluorocarboxylic acid chlorides with ethyl vinyl ether instead of acid anhydrides, in order to prepare a number of β -alkoxyvinyl alkyl ketones with various fluoro-containing substituents of different length and branching, as well as a different number of fluorine atoms.

We have found that ethyl vinyl ether reacts easily with polyfluorocarboxylic acid chlorides at -10° C in the presence of pyridine to give β -ethoxyvinyl polyfluoroalkyl ketones **2–6** in moderate to high yields (56–83%) (Scheme 1). The yield of difluoromethyl-containing enone **2** was lower (40%). The presence of a fluorosulfonyl group in compound **6** does not require significant changes of the reaction conditions and did not significantly lower the yield of the final product.

Compounds 2–4 and 6 are slightly colored liquids, whereas compound 5 (which was synthesized previously by another method⁵) is a colorless crystalline compound. Similarly to the enone 1, enones 2–6, are stable compounds and were stored at 0–4°C for 1 year without changes. We tried unsuccessfully to carry out acylation or monofluoroacylation of ethyl vinyl ether by the corresponding acid chlorides. The similar tendency has been also previously described for the reaction of 2,2dimethoxypropane with chloro-substituted acetic acid anhydrides or chlorides.⁶

The structures of the fluorinated enones 2-6 were assigned by elemental analysis and ¹H and ¹⁹F NMR data (Tables 1, 2). Previously it was found that enone **1** exists in the *trans*-configuration,⁴ here the NMR spectral data of compounds 2-6 also showed that the vinyl group has a *trans*-configuration (the coupling constant of the olefinic protons $J\approx 12$ Hz, Table 1). By taking into account the chemical shift of β -carbon atom signal (¹³C NMR spectra) it is possible to evaluate the electron withdrawing properties of different substituents at the carbonyl group. Selected ¹³C NMR data of enones 1-5 and two related compounds, containing methyl and trichloromethyl groups, are given in the Table 3 (entries 1, 4). Thus, com-



Scheme 1

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Product	R	Yield (%)	d Bp (°C) (P, Hg mm)	Found (%)			Formula	Calc. (%)		
				C	Н	F	_	C	Н	F
2	CHF ₂	40	66 (13)	48.10	5.41	25.31	$C_6H_8F_2O_2$	48.00	5.37	25.31
3	C_2F_5	77	62 (13)	38.61	3.31	43.59	$C_7H_7F_5O_2$	38.55	3.23	43.55
4	C_3F_7	83	69–70 (15)	35.90	2.57	49.63	$C_8H_7F_7O_2$	35.84	2.63	49.60
5	CH(CF ₃) ₂	56	82–83 (15)	38.48	3.11	45.66	$\mathrm{C_8H_8F_6O_2}$	38.41	3.22	45.57
6	CF_2SO_2F	64	67 (02)	30.89	3.57	25.05	$C_6H_7F_3O_4S$	31.04	3.04	24.50

Table 1 Yields, Physical Properties and Elemental Analysis Data for Enones 2-6

 Table 2
 ¹H and ¹⁹F NMR^{a,b} Spectral Data for Enones 2–6

Product	R	$H_{\alpha}(\delta)$	$H_{\beta}\left(\delta\right)$	$J_{({\rm H}\alpha{\rm H}\beta)}({\rm Hz})$	¹⁹ F (δ), <i>J</i> (Hz)
2	CHF ₂ ^c	5.85 d	7.83 d	12.5	-126.36 (d, $J_{\rm HF} = 54.5$, CHF ₂)
3	C_2F_5	5.96 d	7.93 d	12.5	–124.50 (s, 2F, CF ₂), –82.70 (s, 3F, CF ₃)
4	C ₃ F ₇	5.97 d	7.94 d	12.2	-127.20 (q, 2F, $J_{FF} = 11.4$, α-CF ₂), -120.50 (s, 2F, β-CF ₂), -83.10 (t, 3F, $J_{FF} = 11.4$, CF ₃)
5	$CH(CF_3)_2^d$	5.80 d	7.81 d	12.2	-75.30 (d, $J_{\rm HF} = 8.0$, CF ₃)
6	CF_2SO_2F	5.94 dt ^e	7.97 d	12.0	-105.77 (dd, 2F, $J_{FF} = 4.0$, CF ₂), 41.60 (t, 1F, $J_{FF} = 4.0$, SO ₂ F)

^a All spectra were obtained in CDCl₃ solutions at 300 and 282.24 MHz (Varian VXR-300)

^b The ethoxy signals for enones 2–6 appear in the range $\delta = 4.00-4.15$ ppm (q, OCH₂) and $\delta = 1.20$ ppm (t, CH₃).

^c δ = 5.77 ppm (t, *J*_{HF} = 54.5 Hz, CHF₂).

^d δ = 3.94 ppm (sept, $J_{\rm HF}$ =8.0 Hz, CH(CF₃)₂]

 $^{\rm e}J_{\rm H\alpha F} = 1.2 ~{\rm Hz}$

paring the data, the increase in the positive charge of the β -carbon atom of enone **2** in comparison with the methyl group ($\Delta\delta\sim3.5$ ppm, entries 1, 2) is due to the higher electron-acceptor character of the difluoromethyl group. The presence of the trifluoromethyl group (compound **1**, entry 3) induces a further shift of the β -carbon atom signal to lower field ($\Delta\delta\sim2.3$ ppm, entries 2, 3). Chemical shifts of β -carbon atoms of other members of this family do not change in such a manner (entries 3–6). Based on the NMR data of compounds **1–6** it is possible to presume that the behaviour of enones **1**, **3–6** will not differ significantly in nucleophilic reactions, whereas the difluoromethyl-containing enone **2** will possess lower reactivity.

Previously we have shown that enone **1** reacts readily with ammonia, primary and secondary amines to yield the corresponding β -aminovinyl trifluoromethyl ketones.³ Indeed, the other enones **2–5** of this series react easily with primary and secondary amines at room temperature in water solution, in the presence of base (such as Na₂CO₃) to

give the enaminones 7-15 with high yields (Scheme 2, Table 4). The reaction of enone 6 with diethylamine in

 Table 3
 Significant ¹³C NMR^a Spectral Data for Enones

Entry	R	СО	CH_{α}	CH_{β}
1	CH ₃	196.24	105.84	162.62
2	CHF ₂	187.35	98.76	166.15
3	CF ₃	180.19	97.74	168.45
4	CCl ₃	180.75	95.82	167.40
5	C_2F_5	182.56	98.87	168.63
6	C_3F_7	181.20	98.69	168.00
7	CH(CF ₃) ₂	182.45	103.69	166.18

^a All the spectra were obtained in CDCl₃ solutions, c = 0.5 mol/L, T = 22 °C at 75.4 MHz (Varian VXR-300).

	COP	DDN	N	la ₂ CO ₃ , H ₂ O,	r.t. or CH	₂ Cl ₂ , -10	°C		_COR
EtO 2-6	+	н ₁ н ₂ и	п —	89	-100%		R ₁ R ₂ Ν 7-15		
R	CHF ₂	C_2F_5	C ₃ F ₇	CH(CF ₃) ₂	CHF ₂	C ₂ F ₅	C ₃ F ₇	CH(CF ₃) ₂	CF ₂ SO ₂ F
R ₁	Н	Н	н	Н	C ₂ H ₅	CH ₃	CH ₃	CH ₃	C ₂ H ₅
R ₂	CH ₃	CH ₃	CH ₃	CH ₃	C ₂ H ₅	CH ₃	CH ₃	CH ₃	C ₂ H ₅
Compd	7	8	9	10	11	12	13	14	15

Scheme 2

dichloromethane at room temperature resulted in substitution of both the ethoxy group and the fluorine atom of the fluorosulfonyl group by a diethylamino group. A decrease of the reaction temperature to -10° C allowed the selective substitution of the ethoxy group by the diethylamino residue to yield the β -diethylaminovinyl fluorosulfonyldifluoromethyl ketone **15** with high yield. The structures of these compounds were assigned by elemental analyses and ¹H and ¹⁹F NMR data (Table 5).

Enaminones **11–15** having two alkyl substituents at the nitrogen atom exist in *trans*-configuration, similarly to trifluoromethyl-containing analogues.³ The structure of monoalkylamino derivatives **7–10** is significantly different because of the strong intramolecular hydrogen bond formation between NH- and C=O groups. The enaminones **8–10** exist in low-polarity solvents (CCl₄, CDCl₃) predominantly (\geq 95%) in the *cis*-configuration ($J \sim$ 7 Hz) containing few percent of the *trans*-isomer ($J \sim$ 12 Hz). The enaminone **7** in CDCl₃ solution exists as a mixture of

cis (88%) and *trans* (12%) isomers. This is probably connected with the decrease of the electron withdrawing properties of the difluoromethyl group compared to trifluoromethyl analogues. The isomer ratio of enaminones **7–10** does not change in the temperature range of 30–60°C according to the NMR spectral data. Previously we have published detailed investigations on the stereochemistry of trifluoromethyl containing enaminones.⁷ More complete investigations of the stereochemistry of enaminones **7–15** depending on the composition and structure of the fluorinated substituents at carbonyl group is now underway.

Taking into account the results we obtained for the reactions of enones 2-6 with amines we did not expect drastic changes in the formation of heterocycles. Consequently, we chose the enones **3** and **6** as examples useful for the synthesis of heterocycles.⁸ The compounds **3** and **6** react with urea under hydrochloric acid catalysis to give the py-

Product	Yield	eld Bp (°C), (P Hg mm)		Found (%)	Formula	Calc. (%)		
	(%)	or Mp (°C), (solvent for crystallization)	С	Н	F	_	С	Н	F
7	89	92 (13)	44.52	5.29	28.23	C ₅ H ₇ F ₂ NO	44.45	5.22	28.12
8	99	73 (15)	35.39	2.84	46.76	C ₆ H ₆ F ₅ NO	35.48	2.98	46.77
9	96	87-89 (15)	33.32	2.30	52.50	C ₇ H ₆ F ₇ NO	33.22	2.39	52.54
10	96	82 (Et ₂ O/hexane, 1:2)	35.88	2.91	48.50	C ₇ H ₇ F ₆ NO	35.76	3.00	48.48
11	92	117 (0.3)	54.36	7.46	21.50	$C_8H_{13}F_2NO$	54.23	7.39	21.44
12	100	50 (pentane)	38.79	3.60	43.73	C ₇ H ₈ F ₅ NO	38.72	3.71	43.75
13	92	57 (pentane)	35.88	2.91	49.77	C ₈ H ₈ F ₇ NO	35.97	3.02	49.78
14	100	43 (Et ₂ O/hexane, 1:2)	38.61	3.54	45.75	$C_8H_9F_6NO$	38.57	3.64	45.75
15	92	106 (Et ₂ O/hexane 1:1)	37.41	5.04	21.74	$C_8H_{12}F_3NO_3S$	37.06	4.67	21.98

Table 4Yields, Physical Properties and Elemental Analysis Data for Enaminones 7–15

Prod-	$H_{\alpha}(\delta)$	$H_{\beta}(\delta)$	NH (δ)	Other Protons (δ)		J (H	R (δ), J (Hz)	
uct					$H_{\alpha}H_{\beta}$	$H_{\beta}NH$	Others	
(Z)- 7	5.30 d	7.04 dd	10.16 br s	5.75 (t, CHF ₂), 3.11 (d, CH ₃)	7.0	13.0	5.0 (CH ₃ NH), 54.0 (CHF ₂)	$-125.71 (d, J_{HF} = 54.0, CHF_2)$
(E)- 7	5.40 d	7.94 dd	6.50 br s	5.76 (t, CHF ₂), 2.86 (d, CH ₃)	12.0	7.0	5.0 (CH ₃ NH), 54.0 (CHF ₂)	-
(Z)- 8	5.44 dt	7.10 dd	10.30 br s	3.20 (d, CH ₃)	7.0	13.4	5.0 (CH ₃ NH)	-
(E)- 8	5.52 dt	7.98 d		2.98 (d, CH ₃)	12.6	7.2	5.0 (CH ₃ NH)	-
(E)- 9	5.40 d	7.10 dd	10.30 br s	3.15 (d, CH ₃)	7.0	14.0	5.0 (CH ₃ NH)	-
(Z)- 9	5.50 d	8.00 dd		2.90 (d, CH ₃)	12.4	7.5	5.0 (CH ₃ NH)	_
(E)- 10	5.20 d	6.95 dd	10.20 br s	3.74 [sept, CH(CF ₃) ₂], 3.10 (d, CH ₃)	7.0	13.4	5.4 (CH ₃ NH) 8.0 (HF),	–75.50 (d, J _{HF} = 8.0, CF ₃)
(E)- 11	5.35 d	7.83 d	-	5.76 (t, CHF ₂), 3.38 q and 3.31 q (CH ₂), 1.27 t and 1.20 t (CH ₃)	12.5	-	7.0 (CH ₂ CH ₃), 53.0 (CHF ₂)	-125.84 (d, $J_{\rm HF} = 53.0$, CHF ₂)
(E)- 12	5.35 d	7.88 d	-	3.22 s and 2.96 s (CH ₃)	12.2	-	-	-
(E) -13	5.30 d	7.90 d	_	3.20 s and 2.95 s (CH ₃)	12.0	-	_	-126.50 (2F, J_{FF} = 11.4, α -CF ₂), -120.3 (s, 2F, β -CF ₂), -83.00 (t, 3F, J_{FF} = 11.4 Hz, CF ₃)
(E)- 14	5.08 d	7.77 d	_	3.79 [sept, CH(CF ₃) ₂], 2.90 s and 3.20 s (CH ₃)	12.2	_	7.8 (HF)	-
(E)- 15	5.43 br d	7.97 d	-	3.48 q and 3.38 q (CH ₂), 1.26 s and 1.32 s (CH ₃)	12.0	-	1.2 (HF)	-104.06 (br d, CF ₂), 39.68 (br t, SO ₂ F)

Table 5 ¹H and ¹⁹F NMR^a Data for Enaminones 7–15

^a All spectra were obtained in CDCl₃ solutions, c = 0.05 mol/L, T = 22 °C at 300 and 282.24 MHz (Varian VXR-300)



Scheme 3

rimidinoles **16** and **17**, respectively, containing C_2F_5 or unexpectedly CF_2SO_3H groups.

Compound **17** is formed as the result of fluorosulfonyl group hydrolysis. Both pyrimidinoles are stable, colorless crystalline compounds. The structures of compounds **16** and **17** were assigned by elemental analysis and ¹H and ¹⁹F NMR data. Pyrimidinole **17** was also characterized as its *S*-benzylthiuronium salt.

In summary, we have synthesized a number of useful fluoro-containing building blocks, by the reaction of ethyl vinyl ether with various fluorinated carboxylic acid chlorides. It was shown that these available and convenient fluorinated enones 2-6 differ insignificantly from enone 1.

Starting materials were of the highest commercial quality and were used without further purification. ¹⁹F NMR chemical shifts are reported in ppm, negative upfield relative to internal CFCl₃; ¹H NMR and ¹³C NMR chemical shifts are reported in ppm, positive downfield relative to internal TMS; spectra were recorded in CDCl₃ at 200 MHz (Bruker WP-200) and 300 MHz (Varian VXR-300). GC analyses were obtained using SE-30 (5%) column (6.3 m). Acid chlorides of polyfluoro carboxylic acids were obtained by reaction of the corresponding acids with PCl₅ and were distilled before use.

Enones 2-6; (*E*)-5-Ethoxy-1,1,1,2,2-pentafluoropent-4-en-3-one (2); Typical Procedure

A solution of pentafluoropropionic acid chloride (18.98 g, 104 mmol) in anhyd CH_2Cl_2 (20 mL) was added to a mixture of ethyl vinyl ether (7.59 g, 107 mmol) and pyridine (8.45 g, 107 mmol) in CH_2Cl_2 (100 mL) under stirring and cooling to $-10^{\circ}C$. The reaction mixture was then stirred for 20 h at 20°C, then H_2O (100 mL) was added, the H_2O phase was extracted with hexane (3 × 100 mL). The combined organic layers were dried (MgSO₄) and the solvent was evaporated. The residue was distilled under vacuum. Yields, physical constants, elemental analysis and NMR data are shown in Tables 1–3.

Enaminones 7-14; 5-Methylamino-1,1,1,2,2-pentafluoropent-4en-3-one (8); Typical Procedure

 Na_2CO_3 (0.33 g, 4 mmol) was added to a mixture of methylamine hydrochloride (0.57 g, 7 mmol) and enone **3** (1.52 g, 7 mmol) in H_2O (5 mL) under stirring at r.t. The mixture was then stirred for 2 h at 20°C and then extracted with Et₂O (3 × 15 mL). The combined ethereal phase was dried (MgSO₄) and the solvent was evaporated. The residue was distilled under vacuum or crystallized. Yields, physical constants, elemental analysis and NMR data are shown in the Tables 4 and 5.

4-Diethylamino-1,1-difluoro-1-fluorosulfobut-3-en-2-one (15)

Enone **6** (10.1 g, 50 mmol) was added to a solution of Et_2NH (3.65 g, 50 mmol) in CH_2Cl_2 (20 mL) under stirring and cooling to 0–10°C. The mixture was stirred for 2 h at r.t. and the solvent was evaporated. The residue was crystallized. Yields, physical constants, elemental analysis, and NMR data are shown in Tables 4 and 5.

4-Pentafluoroethyl-2-pyrimidinol (16)

12 N aq HCl (1 mL) was added to a mixture of urea (0.90 g, 15 mmol), enone **3** (1.78 g, 8.2 mmol) and EtOH (5 mL) and the mixture was stirred for 24 h at r.t. The solvent was evaporated and the residue was treated with MeCN (5 mL). The precipitate was filtered off and dried. The yield of pure compound **16** was 1.5g (85%), mp 178°C (MeCN, decomposition).

Anal: $C_6H_3F_5N_2O$ (214.09): Calc C, 33.66; H, 1.41; F, 44.39. Found: C, 33.57; H, 1.37; F, 44.32.

¹H NMR (CD₃OD, 200 MHZ): $\delta = 6.90$ [d, 1H, ³ $J_{(H,H)} = 6.3$ Hz, H₅], 8.47 [d, 1H, ³ $J_{(H,H)} = 6.3$ Hz, H₆].

Difluoro(2-hydroxy-4-pyrimidinyl)methanesulfonic Acid (17)

12 N aq HCl (1 mL) was added to a mixture of urea (3.60 g, 60 mmol), enone **6** (12.69 g, 60 mmol) and EtOH (5 mL). The mixture was stirred for 24 h at r.t. The solvent was evaporated and the residue was treated with MeCN (5 mL). The precipitate was filtered off and dried. The yield of pure compound **17** was 0.72g (58%), mp 270°C (decomposition). The *S*-benzylthiuronium salt decomposed at 240-250°C.

Anal: $C_{13}H_{14}F_2N_4O_4S_2$ (392.13): Calc C, 39.82; H, 3.58; F, 9.69. Found: C, 39.61; H, 3.55; F, 9.61.

¹H NMR (CD₃OD, 200 MHz): δ = 7.25 [d, 1H, ${}^{3}J_{(H,H)}$ = 6.2 Hz, H₅], 8.73 [d, 1H, ${}^{3}J_{(H,H)}$ = 6.2 Hz, H₆].

¹⁹F NMR (CD₃OD, 188.28 MHz): $\delta = -109.6$ (s).

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