Synthesis and Properties of β-Cyanovinyl Polyhaloalkyl Ketones

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Abstract: A number of β-cyanovinyl polyhaloalkyl ketones were prepared by the reaction of readily accessible 2-ethoxy-4-trimethylsiloxy-4-polyhaloalkylbut-3-ene nitriles with sulfuric acid. It was demonstrated, that β-cyanovinyl trifluoromethyl ketone, are useful fluorinated building blocks susceptible to 1,2- and 1,4-addition reactions.

Key words: eliminations, α,β-unsaturated ketones, fluorinated compounds, cycloadditions, heterocycles

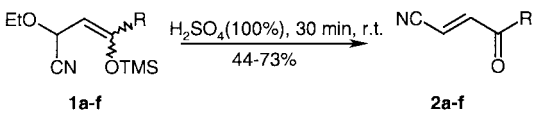
Fluorine containing organic compounds, in comparison to non-fluorinated analogs, quite often exhibit a better set of physical/chemical properties and a higher biological activity. These reasons stimulated an increased interest in the synthesis of fluorine-containing compounds in the last few years.[1] The most common and attractive synthetic method for preparing fluorine-containing compounds, besides direct fluorination, is using available fluorine-containing building blocks as starting materials.[2]

Previously, we have shown that cyano(trimethyl)silane (TMSCN) reacts with various β-alkoxyvinyl polyhaloalkyl ketones to give 1,4-adducts in high yields.[3,4] The obtained 1,4-adducts can be considered as trimethylsilyl ethers of the enol form of corresponding β-alkoxy ketones. One of the inherent properties of β-alkoxy ketones is, they are known to undergo alcohol elimination with the formation of α,β-unsaturated ketones. An application of this reaction would allow the corresponding β-cyanovinyl haloalkyl ketones to be obtained in one step. They are attractive polyfunctional electrophilic fluorine-containing building blocks for further synthetic purposes. α,β-Unsaturated ketones with electron acceptor substituents in β-position are well known to be widely applied in organic synthesis, e.g. in cycloaddition reactions.[5–7] The introduction of halogen atoms into the acyl residue of β-cyano-α,β-unsaturated ketones should increase the electrophilicity of the conjugated system and the specific reactivity of these compounds in reactions such as Diels–Alder addition and nucleophilic addition to the carbonyl group.

In this paper we describe the synthesis of β-cyanovinyl polyfluoroalkyl ketones and some reactions of these previously unknown substances.

As was shown earlier, the adduct of the reaction of β-methoxyvinyl methyl ketone with TMSCN is unstable under the conditions of the addition process at high temperature or in the presence of Lewis acid catalysts and undergoes elimination of TMSOMe to yield a β-cyanovinyl methyl ketone[4] (cf. Scheme 1, R = Me). In contrast to this compound, the adducts **1a**–**f** with R = polyhaloalkyl groups are stable under these reaction conditions. We assumed that the use of Brönsted acids as catalysts allows to realize the synthesis of β-cyanovinyl polyhaloalkyl ketones **2a**–**f** from 1,4-adducts **1a**–**f** by elimination of TMSOEt at ambient temperature. The most readily available trifluoromethyl compound **1a** was used as model substance to find optimal conditions for the synthesis of the desired ketones **2**.

We have found that the action of catalytic amounts of sulfuric, trifluoroacetic, trifluoromethylsulfonic, or perchloric acid to 1,4-adduct **1a** results in the formation of a complex mixture of compounds, containing <15% β-cyanovinyl ketone **2b** at 70–100% conversion by ^{1}H and ^{19}F NMR spectra. The highest yield of the ketone **2b** was obtained using 100% sulfuric acid. Variation of the H_2SO_4/**1b** ratio showed that the yield of ketone **2b** increases with an increase in quantity of sulfuric acid, and with the use of 3–4 equivalents of H_2SO_4, ketone **2b** was the major product of the reaction. This ratio is optimal and was applied by us to synthesize the other ketones **2a**,**c**–**f** (Scheme 1).



1a-f **2a-f**

1, 2	a	b	c	d	e	f
R	CHF_2	CF_3	C_2F_5	C_3F_7	$CH(CF_3)_2$	CCl_3

Scheme 1

The yields of ketones **2a**–**f** were determined after extraction of the reaction mixture with $CDCl_3$ by ^{1}H NMR spectra with a standard quantity of dibromomethane as reference substance. According to these data the obtained extracts of the products contain <3% of other products with a polyhaloalkyl group. In addition, in the ^{1}H NMR spectra of $CDCl_3$ extracts there are signals of ethoxy (4.3 and 1.4 ppm) and trimethylsilyloxy (0.4 ppm) groups with an integral intensity, which is in approximately equal ratio with the intensity of the signals of the ketones **2a**–**f**. Comparison of these data with ^{1}H NMR spectrum of the TMSOEt allows to suppose that these signals are caused by the formation of ethyl and trimethylsilyl sulfates during the reaction. ^{1}H NMR spectrum of $CDCl_3$ extract after

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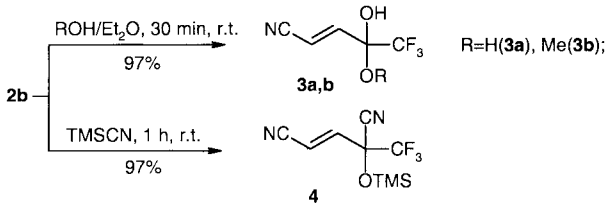
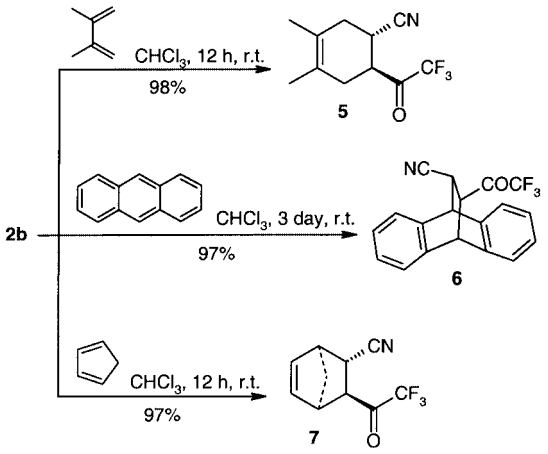
the model reaction between TMSOEt and H_2SO_4 was similar to the above mentioned.

β-Cyanovinyl polyhaloalkyl ketones **2a–f** are formed as single isomers with (*E*)-configuration as shown by the coupling constants of vinyl protons J_{HH} = 16.1–16.4 Hz (Table 1) in the ^{1}H NMR spectra. The ketones can be also isolated by distillation, which was shown by isolation of ketone **2b** in the pure state. Liquid β-cyanovinyl trifluoromethyl ketone **2b** is stable for a long time at room temperature in the absence of moisture and easily adds water and methanol to yield adducts **3a**,**b**, respectively (Scheme 2). The high electrophilicity of the carbonyl group in ketone **2b** was also demonstrated by a fast 1,2-addition reaction with cyano(trimethyl)silane, which proceeds in the absence of a catalyst, to give 1,3-dicyano-1-trifluoromethyl-1-trimethylsiloxypentene (**4**) in high yield. According to the ^{1}H and ^{19}F NMR spectra, it was shown that the C=C bond in compounds **3a** and **4** retains (*E*)-configuration.



Scheme 2

The ketone **2b** was also introduced as dienophile into Diels–Alder reactions with 2,3-dimethylbuta-1,3-diene, anthracene, and cyclopentadiene. Whereas the non-fluorinated *trans*-β-cyanovinyl methyl ketone reacts with 2,3-dimethylbuta-1,3-diene only on heating,[5] the ketone **2b** gives the corresponding cycloaddition products **5**,**6**, and **7** in almost quantitative yields even at room temperature (Scheme 3).



Scheme 3

With respect to the stereospecificity of the Diels–Alder reaction, taking into account the (*E*)-configuration of the ketone **2b** and the ^{1}H and ^{19}F NMR spectra of the obtained compounds, it is possible to prove that the CN and CF_3CO groups in adducts **5**–**7** are in a *trans*-configuration. Adducts **5** and **6** are formed as a single isomer, and adduct **7** is obtained as a mixture of *endo*- and *exo*-isomers in a 7:1 ratio.

We have also shown that the ketone **2b** is active as diene in hetero-Diels–Alder reaction with alkyl vinyl ethers. Thus, interaction of the ketone **2b** with ethyl vinyl ether and 2,3-dihydrofuran results in the formation of adducts **8** and **9**, respectively, in high yields (>97%) and with high diastereoselectivity (de ~88%) (Scheme 4).

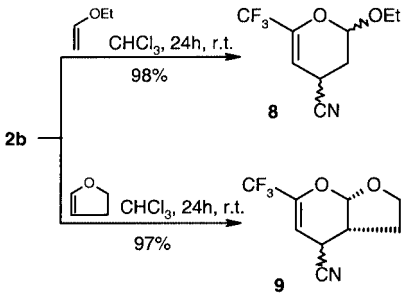
All compounds **5**, **7**–**9** are liquids stable for a long time at room temperature in the absence of moisture.

In summary, we have developed a simple method to prepare β-cyanovinyl polyhaloalkyl ketones **2a**–**f**. The high reactivity of these compounds was demonstrated by 1,2-addition reactions with the carbonyl group and [4+2] cy-

Table 1 Yield and NMR Spectra of Ketones **2a**–**f**

Entry	Product	Yield[a] (%)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz) C*H*COR	CHCN	Others	^{19}F NMR ($CDCl_3$/$CFCl_3$) δ
1	**2a**	44	7.27 (dt, *J* = 16.4, 1.0)	6.62 (d, *J* = 16.4)	5.98 (t, 1 H, *J* = 53.3)	–127.96 (br d, *J* = 53.3)
2	**2b**	60[b]	7.26 (dq, *J* = 16.3, 0.6)	6.71 (d, *J* = 16.3)	-	–78.63 (br s)
3	**2c**	52	7.33 (dt, *J* = 16.3, 1.2)	6.71 (d, *J* = 16.3)	-	–124.41 (br m, 2 F), –82.23 (br s, 3 F)
4	**2d**	45	7.32 (d br t, *J* = 16.2, ≈1.0)	6.70 (d, *J* = 16.2)	-	–126.96 (s, 2 F), –122.53 (br q, 2 F, *J* = 8.5), –80.94 (t, 3 F, *J* = 8.5)
5	**2e**	73	7.18 (d, *J* = 16.1)	6.56 (d, *J* = 16.1)	4.41 (hept, 1 H, *J* = 7.6)	–63.34 (d, *J* = 7.6)
6	**2f**	61	7.61 (d, *J* = 16.1)	6.77 (d, *J* = 16.1)	-	-

[a] NMR yield.
[b] Isolated yield: 53%.



Scheme 4

cloaddition reactions with dienes and vinyl ethers. The high electrophilicity of the conjugated C=C–C=O system opens a possibility to use these compounds as building blocks containing polyfluoroalkyl units.

^{1}H, ^{13}C, and ^{19}F NMR spectra were measured at 300, 75.43, and 282.24 MHz (Varian VXR-300), respectively, in $CDCl_3$ solution (unless otherwise noted) using TMS and $CFCl_3$ as the internal standards. Adducts **1a**–**f** were prepared according to the literature procedure.[4] 100% H_2SO_4 was obtained by mixing of 36 g of 95% H_2SO_4 and 40 g of 20% oleum. Other reagents were purchased from Aldrich. Satisfactory microanalyses were obtained for all new compounds: C, ±0.24; H, ±0.19; N, ±0.17.

Ketones 2a–f from Adducts 1a-f; General Procedure

To 100% H_2SO_4 (0.196 g, 2 mmol) was added the adduct **1a**–**f** (0.5 mmol) under stirring. After 30 min the product was extracted with $CDCl_3$ (3 × 0.5 mL). To the combined extracts were added CH_2Br_2 (0.045 g, 0.26 mmol) as standard. The yields were detected by ^{1}H NMR spectra as a ratio of the integrated intensity of vinyl protons signals of ketones **2a**–**f** and protons of CH_2Br_2 (Table 1).

(*E*)-5,5,5-Trifluoro-4-oxopent-2-enenitrile (2b)

To 100% H_2SO_4 (19.6 g, 200 mmol) was added the adduct **1b** (13.35 g, 50 mmol) under stirring. After 30 min the product was distilled from the reaction mixture in vacuo (0.5 mmHg) at a trap, cooled by liquid nitrogen. At the end of the distillation the temperature of the flask was raised up to 50–60 °C. Crude ketone **2b** was redistilled at atmospheric pressure, with careful protection from moisture; yield: 3.95 g (53%); bp 130–132 °C

^{13}C NMR: δ = 115.14 (s), 115.70 (q, J_{CF} = 289.3 Hz), 117.48 (s), 136.38 (s), 178.48 (q, J_{CF} = 38.5 Hz). IR (CH_2Cl_2): 1744 (C=O), 1616 cm^{-1} (C=C).

(*E*)-5,5,5-Trifluoro-4,4-dihydroxypent-2-enenitrile (3a); Typical Procedure

To a solution of the ketone **2b** (0.45 g, 3.0 mmol) in Et_2O (6 ml) was added H_2O (0.09 g, 5.0 mmol). Then the mixture was stirred for 30 min. The solvent and excess of H_2O were removed in vacuo (Table 2).

Table 2 Yield and NMR Spectra of Compounds **3a**,**b** and **4**–**9**

Product	Yield (%)	Mp (°C) or bp (°C/mm Hg)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{19}F NMR ($CDCl_3$/$CFCl_3$) δ
3a[a]	>97	112–113	6.25 (d, 1 H, *J* = 16.2), 6.91 (dq, 1 H, *J* = 16.2, 0.6), 6.91 (br s, 2 H)	–83.86 (d, *J* = 0.6)
3b[a]	>97	97–99	3.23 (s, 3 H), 6.25 (d, 1 H, *J* = 16.2), 6.86 (d, 1 H, *J* = 16.2), 8.18 (s, 1 H)	–84.96 (br s)
4	97 (85)[b]	88–90/14	0.34 (s, 9 H), 6.08 (d, 1 H, *J* = 16.1), 6.67 (dq, 1 H, *J* = 16.1, ≈0.6)	–79.49 (br s)
5	98	oil	1.66 (br s, 6 H), 2.12 (m, 1 H), 2.32–2.54 (m, 3 H), 3.06 (ddd, 1 H, *J* = 10.1, 10.1, 6.1), 3.37 (ddd, 1 H, *J* = 10.1, 10.1, 5.5)	–78.02 (br s)
6	97	152–153 (hexane)	3.55 (dd, 1 H, *J* = 4.9, 2.5), 3.65 (dd, 1 H, *J* = 4.9, 2.3), 4.67 (br d, 1 H, *J* = 2.5), 4.82 (br s, 1 H), 7.14–7.52 (m, 8 H)	–76.08 (s)
7[c]	97 (84)[b]	96–98/7	major: 1.79 (dm, 1 H, *J* = 9.5), 1.88 (br d, 1 H, *J* = 9.5), 2.85 (dd, 1 H, *J* = 4.1, 1.8), 3.40 (br s, 1 H), 3.62 (br s, 1 H), 3.73 (dd, 1 H, *J* = 4.1, 4.0), 5.93 (dd, 1 H, *J* = 5.5, 2.8), 6.29 (dd, 1 H, *J* = 5.5, 3.2) minor:[d] 1.45 (dm, 1 H, *J* = 9.8), 1.58 (dm, 1 H, *J* = 9.8), 3.06 (br m, 1 H), 3.35 (br m, 1 H), 6.46 (br d, 1 H, *J* = 5.8), 6.59 (dd , 1 H, *J* = 5.8, 2.9)	major: –77.47 (br s) minor: –77.46 (br s)
8[c]	98 (82)[b]	123–125/17	major: 1.27 (t, 3 H, *J* = 7.0), 2.08 (ddd, 1 H, *J* = 14.2, 7.3, 2.3), 2.35 (ddd, 1 H, *J* = 14.2, 3.8, 2.5), 3.44 (m, 1 H), 3.67 (dq, 1 H, *J* = 9.5, 7.0), 3.89 (dq, 1 H, *J* = 9.5, 7.0), 5.35 (dd, 1 H, *J* = 2.5, 2.3), 5.56 (br d, 1 H, *J* = 4.8) minor:[d] 1.21 (t, 3 H, *J* = 7.0)	major: –73.76 (d, *J* = 1.6) minor: –73.68 (d, *J* = 2.4)
9[c]	97 (79)[b]	106–108/0.5	major: 2.03 (m, 1 H), 2.37 (m d, 1 H, *J* = 2.7), 2.81 (m, 1 H), 3.94 (m, 1 H), 4.12 (ddd, 1 H, *J* = ≈9.0, ≈8.8, 7.6), 4.30 (ddd, 1 H, *J* = ≈9.2, ≈9.0, 2.7), 5.40 (br m, 1 H), 5.54 (d, 1 H, *J* = 3.6) minor:[d] 3.48 (m, 1 H), 5.44 (br d, 1 H, *J* = 5.3), 5.66 (br d, 1 H, *J* = 3.7)	major: –73.66 (d, *J* = 2.5) minor: –73.70 (d, *J* = ≈ 1.5)

[a] ^{1}H and ^{19}F NMR spectra were measured in acetone-d_6 (**3a**) or DMSO-d_6 (**3b**).
[b] Yield after distillation, ratio of isomers not changed.
[c] Mixture of isomers, ratio: 7:1 (for **7**), 16:1 (for **8**), 15:1 (for **9**).
[d] The signals are not overlapped by signals of the major isomer.

(*E*)-5,5,5-Trifluoro-4-hydroxy-4-methoxypent-2-enenitrile (3b)
Prepared from the ketone **2b** (0.45 g, 3.0 mmol) and anhyd MeOH (0.16 g, 5.0 mmol) following the typical procedure described for **3a** (Table 2).

(*E*)-4-Trifluoromethyl-4-trimethylsilyloxypent-2-enedinitrile (4)
To TMSCN (0.69 g, 7 mmol) was added the ketone **2b** (0.75 g, 5 mmol). The mixture was allowed to stand for 1 h. Excess of TMSCN was removed in vacuo. Additional purification of **4** can be achieved by vacuum distillation (Table 2).

(*E*)-3,4-Dimethyl-6-trifluoroacetylcyclohex-3-ene-1-carbonitrile (5)
To a solution of 2,3-dimethylbuta-1,3-diene (0.22 g, 2.6 mmol) in $CHCl_3$ (6 mL) was added the ketone **2b** (0.30 g, 2.0 mmol) under stirring and the mixture was allowed to stand for 12 h at r.t. The solvent and excess of 2,3-dimethylbuta-1,3-diene were removed in vacuo (Table 2).

(*E*)-16-(Trifluoroacetyl)tetracyclo[6.6.2.0^{2,7}.0^{9,14}]hexadeca-2(7),3,5,9(14),10,12-hexaene-15-carbonitrile (6)
To a suspension of anthracene (0.54 g, 3 mmol) in $CHCl_3$ (15 mL) was added the ketone **2b** (0.60 g, 4 mmol) with stirring and under argon. Then the mixture was stirred for 3 d at 20 °C. The solvent and excess **2b** were removed in vacuo (Table 2).

3-(Trifluoroacetyl)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (Mixture of Isomers) (7)
To a solution of the ketone **2b** (0.75 g, 5 mmol) in $CHCl_3$ (10 mL) was added a solution of cyclopentadiene (0.33 g, 5 mmol) in $CHCl_3$ (2 mL) under stirring. The mixture was allowed to stand for 12 h at r.t. and then the solvent was removed in vacuo. Additional purification of **7** can be achieved by vacuum distillation (Table 2).

2-Ethoxy-6-trifluoromethyl-3,4-dihydro-2*H*-4-pyrancarbonitrile (Mixture of Isomers) (8); Typical Procedure
To a solution of ethyl vinyl ether (0.50 g, 7 mmol) in $CHCl_3$ (10 mL) was added the ketone **2b** (0.75 g, 5 mmol) under stirring, and then the mixture was allowed to stand for 1 day at r.t. The solvent and excess of vinyl ether were removed in vacuo. Additional purification of **8** can be achieved by vacuum distillation (Table 2).

6-Trifluoromethyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-4-carbonitrile (Mixture of Isomers) (9)
Prepared from 2,3-dihydrofuran (0.49 g, 7.0 mmol) following the typical procedure described for **8**. (Table 2).

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