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

Synthesis and Properties of β-Cyanovinyl Polyhaloalkyl Ketones

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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.3–5 The introduction of halogen atoms into the acyl residue of β-cyanovinyl 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 ketone4 (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 Brønsted 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 1H and 19F NMR spectra. The highest yield of the ketone 2b was obtained using 100% sulfuric acid. Variation of the H2SO4/1b 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 H2SO4, 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).

The yields of ketones 2a–f were determined after extraction of the reaction mixture with CDCl3, by 1H 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 1H NMR spectra of CDCl3 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 1H NMR spectrum of the TMSOEt allows to suppose that these signals are caused by the formation of ethyl and trimethylsilyl sulfates during the reaction. 1H NMR spectrum of CDCl3 extract after
The model reaction between TMSOEt and H₂SO₄ 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 ¹H 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 ¹H and ¹⁹F 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,² the ketone 2b gives the corresponding cycloaddition products 5, 6, and 7 in almost quantitative yields even at room temperature (Scheme 3).

With respect to the stereospecificity of the Diels–Alder reaction, taking into account the (E)-configuration of the ketone 2b and the ¹H and ¹⁹F NMR spectra of the obtained compounds, it is possible to prove that the CN and CF₃CO 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
<th>¹H NMR (CDCl₃/TMS) δ, J (Hz)</th>
<th>¹⁹F NMR (CDCl₃/CFCl₃) δ</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(%)</td>
<td>CHCOR CHCN Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2a</td>
<td>44</td>
<td>7.27 (dt, J = 16.4, 1.0) 6.62 (d, J = 16.4) 5.98 (t, 1 H, J = 53.3)</td>
<td>-127.96 (br d, J = 53.3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>60⁸</td>
<td>7.26 (dq, J = 16.3, 0.6) 6.71 (d, J = 16.3) -</td>
<td>-78.63 (br s)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>52</td>
<td>7.33 (dt, J = 16.3, 1.2) 6.71 (d, J = 16.3) -</td>
<td>-124.41 (br m, 2 F), -82.23 (br s, 3 F)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>45</td>
<td>7.32 (dq t, J = 16.2, 1.0) 6.70 (d, J = 16.2) -</td>
<td>-126.96 (s, 2 F), -122.53 (br q, 2 F, J = 8.5), -80.94 (t, 3 F, J = 8.5)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>73</td>
<td>7.18 (d, J = 16.1) 6.56 (d, J = 16.1) 4.41 (hept, 1 H, J = 7.6)</td>
<td>-63.34 (d, J = 7.6)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>61</td>
<td>7.61 (d, J = 16.1) 6.77 (d, J = 16.1) -</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

¹NMR yield.
²Isolated yield: 53%.
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.

\[ \text{1H, 13C, and 19F NMR spectra were measured at 300, 75.43, and 282.24 MHz (Varian VXR-300), respectively, in CDCl}_3 \text{ solution (unless otherwise noted) using TMS and CFCl}_3 \text{ as the internal standards. Adducts 1a-f were prepared according to the literature procedure.} \]

\[ \text{To 100\% H}_2\text{SO}_4 \text{ (0.196 g, 2 mmol) was added the adduct 1a–f (0.5 mmol) under stirring. After 30 min the product was distilled from the reaction mixture in vacuo (0.5 mmHg) at a trap, cooled by liquid nitrogen. At the end of the distillation the temperature of the flask was raised up to 50–60°C. Crude ketone 2b was redistilled at atmospheric pressure, with careful protection from moisture; yield: 3.95 g (53\%); bp 130–132°C.} \]

\[ \text{ Ketones 2a–f from Adducts 1a–f; General Procedure} \]

To 100\% H\textsubscript{2}SO\textsubscript{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.

\[ \text{1C NMR:} \delta = 115.14 (s), 115.70 (q, \text{J}_\text{CF} = 289.3 \text{ Hz}), 117.48 (s), 136.38 (s), 178.48 (q, \text{J}_\text{CF} = 38.5 \text{ Hz}). \text{ IR (CH\textsubscript{3}Cl\textsubscript{3}):} 1744 (C=O), 1616 \text{ cm}^{-1} (C=C). \]

\[ \text{(E)-5,5,5-Trifluoro-4-oxopent-2-enenitrile (2b)} \]

To a solution of the ketone 2b (0.45 g, 3.0 mmol) in Et\textsubscript{2}O (6 ml) was added H\textsubscript{2}O (0.045 g, 0.26 mmol) as standard. The yields were detected by \textsuperscript{1}H NMR spectra as a ratio of the integrated intensity of vinyl protons signals of ketones 2a–f and protons of CH\textsubscript{3}Br\textsubscript{2} (Table 1).

\[ \text{(E)-5,5,5-Trifluoro-4,4-dihydroxypent-2-enenitrile (3a); Typical Procedure} \]

To a solution of the ketone 2b (0.45 g, 3.0 mmol) in Et\textsubscript{2}O (6 ml) was added H\textsubscript{2}O (0.045 g, 0.26 mmol). Then the mixture was stirred for 30 min. The solvent and excess of H\textsubscript{2}O were removed in vacuo (Table 2).

\[ \text{Synthesis of \textbeta-Cyanovinyl Polyhaloalkyl Ketones} \]
(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-trimethylsilyloxygen-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$^{2,7}.0^{3,4}]$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-2H-4-pyranocarbonitrile (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-4H-furo[2,3-b]pyrano-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).

References