A new synthesis of trifluoromethylated cyclohexenes

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Abstract

1,3-Dimethyl-2-ethoxycarbonyl-1-(trifluoromethyl)cyclohex-4-ene is prepared by the cycloaddition of 1,1,1-trifluoro-2-methyl-2-butenoic acid ethyl ester with 1,3-pentadiene. The dienophile is prepared by the reaction of $CF_3C(O)CH_3$ with $BrCH_2C(O)OC_2H_5$ in the presence of $(C_6H_5)_3Sb$ or $(C_6H_5)_3As$. An extension of this procedure to hexafluoroacetone has provided 1,1,1-trifluoro-2-hydroxy-2-(trifluoromethyl)-4-butanoic acid ethyl ester.

Introduction

Although trifluoromethylated cyclohexenes represent a class of important compounds, for instance as key intermediates in the synthesis of fluoro-functionalized natural products, only a few examples have been described in the recent literature [1–3].

2,6-Dimethyl-6-(trifluoromethyl)-1-cyclohexene-carbaldehyde [1, 2] and 6,6-dimethyl-2-(trifluoromethyl)-1-cyclohexene-carbaldehyde [3] are crucial building blocks in the synthesis of larger structures containing a trifluoromethylated cyclohexene unit. Hence the aim of this work was the synthesis of 1,3-dimethyl-2-ethoxycarbonyl-1-(trifluoromethyl)cyclohex-4-ene (**3**) as a building block.

Results

Since trifluoroacetone undergoes an aldol condensation even in the presence of weak bases such as KCN [5] or $(n\text{-}C_4H_9)_3P$ to yield 1,1,1,5,5,5-hexafluoro-2-hydroxy-2-methyl-pentane-4-one [4], olefination was carried out according to the method of Huang *et al.* [6] by reacting a mixture of triphenylstibine and bromoacetic acid ethyl ester with trifluoroacetone to yield **1**† according to:

$$BrCH_2C(O)OC_2H_5 + CF_3C(O)CH_3 + (C_6H_5)_3Sb \longrightarrow CH_3C(CF_3)=CHC(O)OC_2H_5 \quad (1)$$
(1)

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†The proposed structures for compounds **1**, **2** and **3** are given in Scheme 1.

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In addition, compound **1** could also made by a modified Wittig reaction through the arsonium salt **4** prepared from triphenylarsine and bromoacetic acid ethyl ester, via deprotonation to the arsorane **5** by potassium t-butanolate and finally condensation with trifluoroacetone according to:

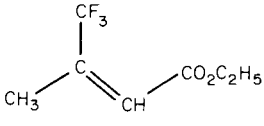
$$(C_6H_5)_3As + BrCH_2CO_2C_2H_5 \longrightarrow [(C_6H_5)_3As{-}CH_2CO_2C_2H_5]^+Br^- \quad \textbf{(4)}$$

$$\textbf{4} + KOC(CH_3)_3 \longrightarrow (C_6H_5)_3As{-}CHCO_2C_2H_5 \quad \textbf{(5)}$$

$$\textbf{5} + CF_3C(O)CH_3 \longrightarrow \textbf{1} + (C_6H_5)_3AsO \quad (2)$$

The structure of **1** was elucidated as the *Z*-form from the recorded mass and ^1H NMR spectra. Such results were independent of the chosen method of synthesis via routes (1) or (2). However, an extension of these procedures to hexafluoroacetone gave compound **2** only.

Cycloaddition of **1** with 1,3-pentadiene over the temperature range 20–150 °C and pressures up to 72 atm did not occur even when Lewis acids such as $BF_3 \cdot OEt_2$ or $TiCl_4$ were added. Only by reacting both substances in a heated sealed tube at 270 °C for 3 d was compound **3** obtained. No hint of other possible regioisomers was observed. A further analysis of the homonuclear ^1H shift correlations in a two-dimensional COSY NMR experiment confirmed the expected half-chair conformation for a cyclohexene derivative.



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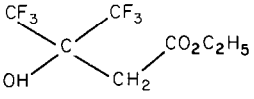

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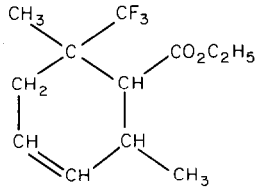

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Scheme 1.

Experimental

Melting points are reported uncorrected. IR spectra were obtained with a Bruker FT spectrometer IFS 85 with solids in a matrix of KBr and liquids as a film between KBr plates. Capillary gas chromatography was performed with a 12.5 m column (SE54) on a Perkin-Elmer 8420 apparatus, while preparative gas–liquid chromatography was undertaken with a packed 3 m column (diameter 6 mm, phase 10% OV 101 on Chromosorb P AW, 60–80 mesh) on a Perkin-Elmer F21 apparatus. NMR spectra were recorded on Bruker WP 80, WP 250 and AM 400 spectrometers. The internal standards

were $CFCl_3$ for ^{19}F and tetramethylsilane for ^1H and ^{13}C NMR spectra. Mass spectra were obtained with a Varian MAT-CH7 apparatus and a Finnigan MAT ion trap, ITD 800.

Ethoxycarbonylmethylenetriphenylarsonium bromide (4)

To a solution of triphenylarsine (100 g, 0.33 mol) in absolute xylene (65 ml) was added bromoacetic acid ethyl ester (75.3 g, 0.45 mol). The reaction mixture was stirred for 1 d at 90 °C. Afterwards compound **4** was filtered off, washed with absolute xylene and dried *in vacuo*.

$[(C_6H_5)_3As-CH_2CO_2C_2H_5]^+Br^-$: yield, 139.25 g (88%); m.p., 157 °C. IR (ν_{max}) [cm^{-1}]: 3045 (s); 3005 (vs); 2985 (vs); 2818 (vvs); 2755 (vs); 1697 (vvs); 1424 (vs); 1303 (vvs); 1182 (vvs); 1152 (vs); 857 (vs); 751 (vvs); 743 (vvs); 691 (vvs). ^1H NMR δ: 1.1 (t, 3H, CH_3); 4.1 (qu, 2H, CH_2); 5.6 (s, 2H, CH_2); 7.6–8.0 (m, 15H, arom. H) ppm. ^{13}C NMR δ: 13.8 (qu, CH_3); 34.6 (t, CH_2); 63.0 (t, CH_2); 121.6 (s, arom. C next to As); 130.8, 133.2, 134.2 (d, arom. C); 165.7 (s, carbonyl C) ppm. MS (*m/z*): no M^+ peak; 306 [$(C_6H_5)_3As^+$, 40%]; 229 [$(C_6H_5)_2As^+$, 32%]; 152 [$C_6H_5As^+$, 100%]; 87 [$(CH_2CO_2C_2H_5)^+$, 4%]; 73 [$(CO_2C_2H_5)^+$, 2%]; 45 [$(OC_2H_5)^+$, 8%]. Analysis: Calcd. for $C_{22}H_{22}O_2AsBr$ (473.2): C, 55.8; H, 4.7%. Found: C, 56.0; H, 4.7%.

Ethoxycarbonylmethylenearsorane (5)

Compound **4** was added in portions at 0 °C to a stirred suspension of KOC_4H_9 (33.67 g, 0.3 mol) in absolute ether (600 ml). Stirring at 0 °C was continued for 3 h. It was most convenient to use this material directly for the reaction with trifluoroacetone. Efforts to obtain arsorane **5** analytically pure failed, but it was possible to record an ^1H NMR spectrum. ^1H NMR δ: 1.1 (t, 3H, CH_3); 4.1 (qu, 2H, CH_2); 4.3 (s, 1H, CH); 7.5–7.9 (m, 15H, arom. H) ppm.

1,1,1-Trifluoro-2-methyl-2-butenoic acid ethyl ester (1)

Method 1

Trifluoroacetone (40.29 g, 0.36 mol) in absolute ether (50 ml) was added to the stirred and cooled suspension of **5** in ether. The reaction mixture was warmed up to room temperature over 2 h and held with stirring for 1 d at this temperature. Triphenylarsine oxide and KBr were filtered and washed three times with small portions of ether. The solution was distilled. After separation of the solvent, the residue was condensed into a trap cooled with liquid N_2. Repeated distillation gave pure **1** Yield, 34.4 g (63%); b.p., 125 °C.

Method 2

Heptane (1.4 ml, 10 mmol) as standard, triphenylstibine (3.85 g, 10.9 mmol), bromoacetic acid ethyl ester (2.00 g, 12 mmol) were filled in and trifluoroacetone (1.05 g, 9.4 mmol) was condensed *in vacuo* into a flame-dried Carius tube fitted with a Teflon valve and a magnetic stirring bar. After heating for 7 h at 100 °C, the reaction mixture was hydrolyzed with aqueous

NaOH (50 ml) and then extracted twice with ether (30 ml). The combined organic phases were neutralized with dilute HCl and finally extracted with saturated aqueous NaCl solution. The organic phase was dried ($MgSO_4$) and filtered. After separation of the solvent, GC analysis of the residue revealed complete conversion of trifluoroacetone and the formation of **1**, identified by comparison with a sample prepared by the former procedure.

$CH_3C(CF_3)=CHC(O)OC_2H_5$: yield, 47%. IR ($\nu_{max}$) [$cm^{-1}$]: 3005 (s); 2941 (m); 1729 (vvs); 1682 (s); 1447 (s); 1371 (s); 1353 (s); 1296 (vs); 1206 (vs); 1192 (vs); 1106 (vs); 1041 (vs); 892 (vs); 635 (s). ^1H NMR δ: 1.3 (t, 3H, $^3J=7.0$ Hz, CH_3); 2.25 (d, 3H, $^4J=1.5$ Hz, CH_3); 4.25 (qu, 2H, $^3J=7.0$ Hz, CH_2); 6.3 (m, 1H, $^4J=1.5$ Hz, vinyl H) ppm. ^{13}C NMR F-coupled δ: 12.3 (qu, CH_3); 14.1 (qu, CH_3); 60.9 (t, CH_2); 121.6 (d, CH, $^1J_{CH}=160.6$ Hz); 116.6, 121.0, 125.3, 129.7 (qu, $^1J_{CF}=274.0$ Hz, CF_3); 141.2, 141.7, 142.1, 142.6 (qu, $^2J_{CF}=30.5$ Hz, vinyl C); 164.9 (s, carboxy C) ppm. ^{19}F NMR δ: -71.8 (s) ppm. MS (*m/z*): 183 [$M^+ + 1$, 87%]; 182 [M^+, 6%]; 163 [$M^+ - F$, 2%]; 154 [$M^+ - C_2H_4$, 17%]; 137 [$M^+ - OC_2H_5$, 100%]; 114 [$(M^+ + 1) - CF_3$, 13%]; 69 [CF_3, 4%]. Analysis: Calcd. for $C_7H_9O_2F_3$ (182.141): C, 46.2; H, 5.0%. Found: C, 46.1; H, 4.8%.

1,3-Dimethyl-2-ethoxycarbonyl-1-(trifluoromethyl)cyclohex-4-ene (3)

A solution consisting of ether (20 ml), dichloromethane (4 ml), 1,3-pentadiene (2 ml, 20 mmol) and **1** (1.82 g, 10 mmol), containing n-heptane additionally as a standard (1.4 ml, 10 mmol), was held over 3 d at 270 °C in a sealed tube. The crude reaction mixture was condensed into a cooled (-196 °C) trap. GC analysis indicated 48% conversion of compound **1**. Further purification was performed by preparative gas–liquid chromatography (160 °C, isotherm; carrier gas, helium; flow rate, 80 ml min^{-1}) to yield a yellowish, fruity smelling liquid (40 mg).

$CH_3C(CF_3)CH_2CH=CHCH(CH_3)CHC(O)OC_2H_5$: IR ($\nu_{max}$) [$cm^{-1}$]: 3027 (s); 2963 (vs); 1737 (vvs); 1665 (m); 1462 (vs); 1376 (s); 1282 (vs); 1218 (vs); 1181 (vvs); 1035 (vs); 692 (vs). ^1H NMR δ: 1.0 (d, 3H, 3-CH_3); 1.2 (m, 6H, 1-CH_3, ester CH_3); 1.9 (m, 1H, 2-CH); 2.1–2.4 (m, 2H, 6-CH_2); 4.2 (d of qu, 2H, ester CH_2); 5.4–5.8 (m, 2H, vinyl H) ppm. ^{13}C NMR δ: 13.90 (ester CH_3 or 3-CH_3); 14.00 (ester CH_3 or 3-CH_3); 19.15 (1-CH_3); 31.12 (2-CH); 32.13 (6-CH_2); 42.72 ($^2J_{CF}=24.4$ Hz, 1-C); 49.65 (3-CH); 60.61 (ester CH_2); 121.60 (4- or 5-CH); 128.50 ($^1J_{CF}=278.6$ Hz, 1-CF_3); 130.83 (4- or 5-CH); 173.23 (carboxy C) ppm. ^{19}F NMR δ: -78.0 (s) ppm. MS (*m/z*): 251 [$M^+ + 1$, 33%]; 250 [M^+, 47%]; 205 [$M^+ - OC_2H_5$, 2%]; 177 [$M^+ - CO_2C_2H_5$, 25%]; 107 [$C_8H_{11}^+$, 100%]; 69 [CF_3, 15%]. A satisfactory elemental analysis of **3** has not been obtained.

1,1,1-Trifluoro-2-hydroxy-2-(trifluoromethyl)-4-butanoic acid ethyl ester (2)

Triphenylstibine (12.11 g, 34.3 mmol) and bromoacetic acid ethyl ester (4.1 ml, 37.7 mmol) were placed in a flame-dried Carius tube fitted with a Teflon valve and a magnetic stirring bar. Hexafluoroacetone (3.95 g, 23.8

mmol) was added *in vacuo* and the reaction mixture was kept at 120 °C with stirring for 5 h. The volatile components were condensed into a cooled (−196 °C) trap and identified as 90% pure **2**. Further purification for analytical purposes was achieved by preparative gas–liquid chromatography (130 °C, isotherm; carrier gas, helium; flow rate, 80 ml min^{-1}).

$(CF_3)_2C(OH)CH_2C(O)OC_2H_5$: IR ($\nu_{max}$) [$cm^{-1}$]: 3343 (vs); 2992 (s); 1716 (vvs); 1448 (vs); 1382 (vs); 1330 (vvs); 1278 (vvs); 1200 (vvs); 1042 (vs); 991 (vs); 704 (vs); 675 (vs). ^1H NMR δ: 1.3 (t, 3H, ester CH_3); 2.85 (s, 2H, CH_2); 4.3 (qu, 2H, ester CH_2); 6.5 (s, 1H, OH) ppm. ^{13}C NMR, F-coupled δ: 14.0 (ester CH_3); 31.4 (CH_2); 63.0 (ester CH_2); 75.1 (m, C−OH, $^2J_{CF}=30.2$ Hz); 118.5, 121.3, 124.2, 127.1 (qu, CF_3, $^1J_{CF}=287.9$ Hz); 171.1 (carboxy C) ppm. ^{19}F NMR δ: −78.8 (s) ppm. MS (*m/z*): 255 [$M^+ + 1$, 38%]; 209 [$C_5H_3O_2F_6^+$, 6%]; 139 [$C_4H_2O_2F_3^+$, 100%]; 111 [$C_3H_2OF_3^+$, 67%]; 69 [CF_3, 6%]; 61 [$C_2H_2OF^+$, 9%]; 60 [C_2HOF^+, 25%]. Analysis: Calcd. for $C_7H_8O_3F_6$ (254.126): C, 33.1; H, 3.1%. Found: C, 33.2; H, 3.1%.

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References

1 Y. Kobayashi, Y. Hanzawa and M. Suzuki, *Tetrahedron Lett.*, *30* (1989) 571.
2 Y. Hanzawa, M. Suzuki, Y. Kobayashi and T. Taguchi, *J. Org. Chem.*, *56* (1991) 1718.
3 Y. Kobayashi, T. Taguchi and A. Hosada, *Tetrahedron Lett.*, *26* (1985) 6209.
4 E. T. McBee, P. H. Campbell and C. W. Roberts, *J. Am. Chem. Soc.*, *78* (1956) 4597.
5 M. Nazario, C. Seoane and J. L. Soto, *Heterocycles*, *27* (1988) 663.
6 Y. Z. Huang, Y. C. Shen and C. Chen, *Tetrahedron Lett.*, *27* (1986) 2903.