# *Articles*

## Preparation of Bis(trifluoromethyl) Compounds via Functionalization of 1,1,1,3,3,5,5,5-Octafluoropentane

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The hydrochlorofluorocarbon $CF_3CH_2CCl_2CH_2CF_3$ (**3**) was prepared from the hydrofluorocarbon $CF_3CH_2CF_2CH_2CF_3$, by a selective Cl−F exchange reaction using $AlCl_3$. Compound **3** was derivatized further to provide novel fluorinated intermediates including $CF_3CH{=}C{=}CHCF_3$, $CF_3CH_2C(O)CH_2CF_3$, and $CF_3CH_2CH(OH)CH_2CF_3$.

### Introduction

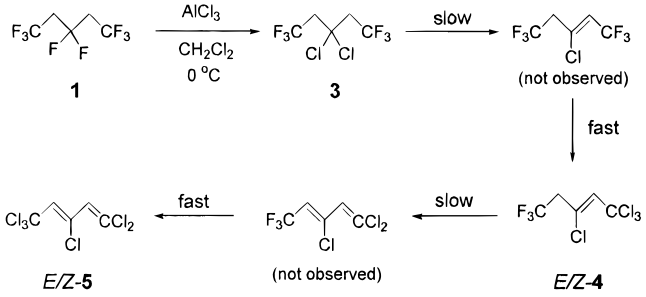
Due to the efforts of the chemical industry to find replacements for chlorofluorocarbons (CFCs), a large number of hydrofluorocarbons[1−5] hydrochlorofluorocarbons,[6,7] and fluorocarbon ethers[8] have been prepared and evaluated for a variety of applications. Several of these, having three or more carbon atoms, have been prepared in pilot-scale quantities. Consequently, several new fluorinated materials are potentially available which may find further application as chemical intermediates. However, since both thermal and chemical stability is a requirement of virtually all CFC replacements, the use of these substitute materials as chemical intermediates requires methodology for convenient functionalization. As there is continued interest in organic compounds bearing trifluoromethyl groups, $CF_3CH_2CF_2CH_2CF_3$ (**1**) was chosen for evaluation as a synthetic intermediate due to the presence of two $CF_3$ groups and its relatively easy synthesis from inexpensive starting materials.

### Results and Discussion

Compound **1**, bp 69−70 °C, has been prepared by a two-step sequence involving the addition of $CCl_4$ to vinylidene chloride to give $CCl_3CH_2CCl_2CH_2CCl_3$, followed by its fluorination with $HF/SbCl_5$.[9]

Octafluoropentane (**1**) is relatively unreactive, being unaffected when treated with triethylamine in DMF at room temperature for 2.5 days or with concd $H_2SO_4$ at 95 °C (20 h), but it did undergo significant dehydrofluorination (to *E*/*Z*-$CF_3CH{=}CFCH_2CF_3$, **2**) in the vapor phase over activated carbon above approximately 300 °C.[10] **1** also reacted with $AlCl_3$ at room temperature to give one volatile product and several high-boiling products. The latter result was not entirely unexpected since selective Cl−F exchange reactions with $AlCl_3$ are fairly rare and are largely limited to compounds in which the exchanged fluorines were activated by virtue of being allylic[11] or on a carbon adjacent to a heteroatom.[12] The selectivity in the reaction of **1** with $AlCl_3$ improved significantly, however, when the exchange was run in $CH_2Cl_2$ at 0 °C (decreasing substantially above 5 °C). The main product was $CF_3CH_2CCl_2CH_2CF_3$ (**3**) (72% yield). The optimum stoichiometry for achieving good conversions at reasonable reaction times at 0 °C was 2 mol of $AlCl_3$/mol of **1**. Monochloroheptafluoropentanes were virtually absent, being detectable only in trace quantities by GC−MS. Major byproducts were *E*/*Z*-$CF_3CH_2CCl{=}CHCCl_3$ (**4**) and *E*/*Z*-$CCl_3CH{=}CClCH{=}CCl_2$ (**5**). Here too, no significant products corresponding to partial exchange of the $CF_3$ fluorines were observed. Thus, effectively, F−Cl exchange occurred one carbon at a time rather than one fluorine at a time. Significantly, **4** and **5** are unsaturated, suggesting that exchange at the $CF_3$ groups does not occur under these conditions until the fluorines become allylic. The proposed sequence shown in Scheme 1 is consistent with these observations. Olefin formation via dehydrochlorination of **3** (or dehydrofluorination of the possible intermediate $CF_3CH_2CFClCH_2CF_3$), leading to $CF_3CH_2CCl{=}CHCF_3$, is believed to be the rate-limiting step for the formation of **4** and **5**. Once allylic, all $CF_3$ fluorines are rapidly exchanged for

**Scheme 1**

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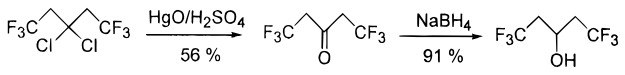
chlorine. A similar observation[13] has been made in the exchange of fluorine for chlorine in 1,2-dichlorohexafluorocyclopentene with $AlCl_3$, which gave perchlorocyclopentene without the detection of intermediate exchange products.

Compound **3** was converted into the novel ketone $CF_3CH_2C(O)CH_2CF_3$ (**6**) with HgO in 100% $H_2SO_4$ (25 °C, 0.75 h, 56% yield). The latter was reduced to the corresponding alcohol (**7**) with aqueous $NaBH_4$ (91% yield). While **6** and **7** possess convenient functionality



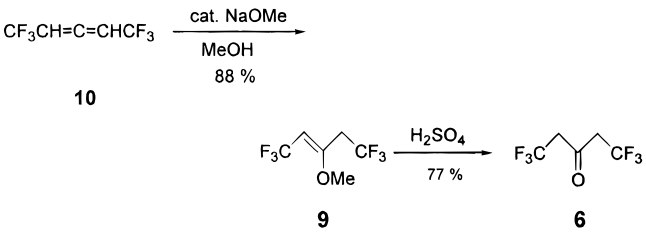

**3** **6** **7**

in addition to two $CF_3$ groups, the use of HgO in the preparation of **6** was environmentally undesirable for large-scale operations. For this reason, focus was directed toward the dehydrochlorination products of **3**, i.e., $CF_3CH{=}CClCH_2CF_3$ (**8**), with the anticipation that conversion of the vinyl chloride to its corresponding vinyl acetate[14] and subsequent hydrolysis would provide the ketone without the need for mercury salts. Alternatively, there was also sufficient precedence[2] to suggest that **8** or **2** might be converted into the vinyl ether $CF_3CH{=}C(OCH_3)CH_2CF_3$ (**9**).

Vapor phase dehydrochlorination of **3** over an activated carbon catalyst at 266 °C resulted in selectivities for *E*/*Z*-**8** of about 95% at 50% conversion. Although the dehydrochlorination of **3** in the liquid phase (1 equiv of $Et_3N$ in DMF) resulted in somewhat lower selectivities for **8** (ca. 80%), conversions were over 90%. It was noted however, that in the early stages of the reaction the principle product was a compound more volatile than either *E*- or *Z*-**8**, but its relative concentration diminished with time so that it was only a minor byproduct at high conversions of **3**. The compound was identified as the novel allene $CF_3CH{=}C{=}CHCF_3$ (**10**).[15]

Allene **10** had signature spectral characteristics typical of allenes, including an IR band at 2004 $cm^{-1}$ and a $^{13}C$ resonance for the central carbon at 207 ppm. However, the $^1H$ NMR spectrum was notable as it consisted of a symmetrical heptet ($J$ = 4.6 Hz, in a 1:6:15:20:15:6:1 ratio), indicating identical coupling constants for $^3J_{H-F}$ and $^5J_{H-F}$. Long-range coupling constants in allene systems are unusually large. For example, $^4J_{H-H}$ values of at least 6.5 Hz have been recorded for $RCH{=}C{=}CH_2$ compounds,[16] while a $^5J_{H-H}$ value of 2.9 Hz was reported for $R_fCH{=}C{=}C(CH_3)_2$.[17] Thus, the simplest explanation for the observed proton spectrum for **10** is that the unusually large $^5J_{H-F}$ value, due to the geometry of the allene system, is coincidentally identical with the normal value observed for $^3J_{H-F}$. This conclusion was further supported by the $^{19}F$ NMR spectrum (282 MHz). The inner peak of the three-peak spectrum, while unresolved and twice the area of each of the two adjacent peaks, had the same *height*, indicating a nonzero, but negligibly small, difference between $^3J_{H-F}$ and $^5J_{H'-F}$.

Consistent with the fact that protonation of **10** at C-3 would result in an allylic cation (following bond rotation) twice destabilized by the $CF_3$ groups on either end of the allylic system, **10** was recovered unchanged after heating




with $H_2SO_4$ for 2 h at 100 °C. In contrast, methanol added across the C=C double bond under mild conditions (10−20 °C) in the presence of a catalytic amount of $NaOCH_3$ to give the methyl vinyl ether **9** in 88% yield. The latter hydrolyzed readily ($H_2SO_4$, 15−20 °C, 0.5 h) to give ketone **6** (77% yield).

Due to the susceptibility of **10** to nucleophilic attack, its synthesis via the double dehydrochlorination of **3** is accompanied by further reaction with organic bases, reducing the yield of **10**. This may explain in part the observation cited above that the amount of allene was initially the main product but a minor product at high conversions of **3** using 1 equiv of $Et_3N$ in DMF. With **2** equiv of triethylamine in DMF at room temperature, **10** was the major product at conversions of **3** ranging from about 10 to 90%, but long reaction times (ca. 2.5 d) were required to achieve conversions of about 90%. Pushing conversions to >85% resulted in a large decrease in the percentage of **10** in the product mixture. A statistically designed set of experiments was conducted to develop a more efficient synthesis which employed a reaction temperature of 60 °C and reaction times of 2.5−3.0 h. Under these conditions, the conversion of **3** was typically 76−79%, while the selectivity for **10** was 79−80% and the selectivity for *E*/*Z*-$CF_3CH{=}CClCH_2CF_3$ was 10−11%. The isolated yield of **10**, based on unrecovered **3**, was 51−52%.

In summary, a selective Cl−F exchange, rarely observed in saturated systems, has permitted the synthesis of **3** from **1** in good yield. **3** was a key intermediate in the preparation of several novel compounds (**6**−**10**) bearing two trifluoromethyl groups in addition to convenient functionality for further synthetic elaboration.

## Experimental Section

**Caution!** Compound **1** was shown to be toxic in an acute inhalation study in mice. During an exposure to 5000 ppm of **1**, all mice died within the first 5 min. It was also clastogenic (mutagenic) in a human lymphocyte study. Based on these findings, care should be exercised when using **1**.

**3,3-Dichloro-1,1,1,5,5,5-hexafluoropentane (3).** To 125 mL of $CH_2Cl_2$, cooled in an ice bath, was added 33.5 g (0.251 mol) of $AlCl_3$, followed by the dropwise addition over 0.5 h of 25.7 g (0.119 mol) of $CF_3CH_2CF_2CH_2CF_3$. Stirring was continued at ice-bath temperature for an additional 5 h before quenching of the reaction by adding the mixture to 500 mL of ice and water. The aqueous layer was extracted with 25 mL of $CH_2Cl_2$, and the combined organic layers were washed with 50 mL of water and dried ($Na_2SO_4$). GC analysis indicated a conversion of 98% and a selectivity of 91%. Distillation gave 21.4 g (72% yield) of >99% pure $CF_3CH_2CCl_2CH_2CF_3$. Bp: 110 °C. $^1H$ NMR: $\delta$ 3.3 (q, $J$ = 9 Hz) ppm. $^{19}F$ NMR: $\delta$ −61.5 (t, $J$ = 9 Hz) ppm. MS: 248 (0.01), 215 (28.8), 213 (85.6), 167

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(12.2), 165 (19.7), 151 (16.2), 149 (51.8), 133 (49.0). Anal. Calcd for $C_5H_4Cl_2F_6$: C, 24.12; H, 1.62. Found: C, 24.08; H, 1.58.

The byproduct *E*/*Z*-$CF_3CH_2CCl{=}CHCCl_3$ had the following properties. Bp: 80−90 °C at 50 mmHg. The following are for the major isomer. $^1$H NMR: $\delta$ 6.74 (s), 3.45 (q, $J$ = 8.5−9.0 Hz) ppm. $^{19}$F NMR: $\delta$ −61.6 (t, $J$ = 8.5−9.0 Hz) ppm. The following are for the minor isomer. $^1$H NMR: $\delta$ 6.94 (s), 3.18 (q, $J$ = 9.5−9.8 Hz). $^{19}$F NMR: $\delta$ −65.1 (t, $J$ = 9.5−9.8 Hz) ppm. The mass spectra for the two isomers, having a weak molecular ion at *m*/*z* 260, were nearly identical.

The byproduct *E*/*Z*-$CCl_3CH{=}CClCH{=}CCl_2$ had the following properties. Bp: 150−151 °C at 47 mmHg. $^1$H NMR: one isomer, 6.94 (s) and 6.41 (s) ppm; other isomer, 6.80 (d, J = 1.7 Hz) and 6.69 (d, J = 1.7 Hz) ppm. The mass spectra for the two isomers were virtually identical: 272 (1.31), 274 (2.0), 276 (1.6), 278 (0.6), 237 (65.7), 239 (100), 241 (67.5), 243 (17.6).

**Vapor Phase Process for the Preparation of 3-Chloro-1,1,1,5,5,5-hexafluoropent-3-ene (8).** $CF_3CH_2CCl_2CH_2CF_3$ (**3**) (13.5 g/h) diluted with nitrogen (25 mL/min) was passed over 50 mL of Darco 12−20 mesh activated carbon at 266 °C. A conversion of 47% was realized with a selectivity for $C_5H_3ClF_6$ isomers of 96%. At 315 °C, the conversion increased to 98%, while the selectivity decreased to 84%. *E*/*Z*-$CF_3CH{=}CClCH_2CF_3$ distilled at 81−92 °C. A distillation cut having a boiling point of 83−85 °C contained the isomers in a 3:1 ratio, which changed to ca. 1:3 at 92−96 °C. Spectra taken on the different distillations cuts allowed assignments to be made. The following are for the lower boiling isomer. $^1$H NMR: $\delta$ 6.21 (1H, q, $J$ = 7 Hz) and 3.4 (2H, q, $J$ = 9 Hz) ppm. $^{19}$F NMR: $\delta$ −59.3 (d, $J$ = 7 Hz) and −64.5 (t, $J$ = 9 Hz) ppm (minor F−F coupling (ca. 2 Hz) also observed). The following are for higher boiling isomer. $^1$H NMR: $\delta$ 6.06 (1H, q, $J$ = 7 Hz) and 3.2 (2H, q, $J$ = 9.6 Hz) ppm. $^{19}$F NMR: $\delta$ −61.3 (d, $J$ = 7 Hz), −65.6 (t, $J$ = 9.6 Hz) ppm. MS: 212 (60.6), 214 (19.3), 193 (26.9), 195 (8.6), 177 (38.9), 113 (96.2), 69 (100). Anal. Calcd for $C_5H_3ClF_6$: C, 28.26; H, 1.42. Found: C, 28.26; H, 1.37.

**3-Chloro-1,1,1,5,5,5-hexafluoropent-3-ene (8) (Liquid Phase Process).** A mixture of 100 mL of dimethylformamide, 24 g of triethylamine, and 50.0 g of $CF_3CH_2CCl_2CH_2CF_3$ was heated to 65−70 °C for 3 h and at 80−90 °C for an additional 2 h. The cooled slurry was poured into 500 mL of cold 0.4 N HCl. The organic layer was separated and washed with 50 mL of water to give 37.5 g of crude product, which by GC analysis indicated a conversion of 92.6% and a selectivity for *E*/*Z*-$CF_3CH{=}CClCH_2CF_3$ of 77%. The higher boiling isomer was obtained in 96% purity from a distillation fraction boiling at 92 °C. The yield of *E*/*Z*-**8**, having a boiling point of 81−93 °C was 22.6 g (53%). A main byproduct was 1,3-bis(trifluoromethyl)allene (**10**).

**1,3-Bis(trifluoromethyl)allene (10).** A mixture of 240 mL of DMF and 48.2 g (0.48 mol) of triethylamine was heated to 59 °C in an oil bath. 59.9 g (0.24 mol) of **3** was added and heating continued for 3.0 h. The reaction was quenched by adding the rapidly cooled reaction mixture to 1 L of cold 0.4 N HCl. The two-phase mixture was cooled to 5−10 °C, and the lower layer (42.0 g) was separated and dried. Distillation provided 19.5 g of 99% pure $CF_3CH{=}C{=}CHCF_3$ (bp 45−46 °C) and 6.6 g of **3** for a yield of 52%, based on unrecovered **3**. FT-IR: 3056, 2004, 1304, 1278, 1255, 1138 cm$^{-1}$. MS: 176 (P, 100). $^{13}$C NMR: $\delta$ 206.8 (m, $J_{C-F}$ = ~6 Hz), 121.6 (q, $J_{C-F}$ = 275.2 Hz), 92.9 (q, $J_{C-F}$ = 39 Hz) ppm. $^1$H NMR: $\delta$ 5.97 (heptet, $J$ = 4.6 Hz) ppm. $^{19}$F NMR: $\delta$ −61.5 (t, $J$ = 4.6 Hz) ppm. Anal. Calcd for $C_5H_2F_6$: C, 34.11; H, 1.14. Found: C, 34.11; H, 1.13.

**Preparation of 1,1,1,5,5,5-hexafluoropentan-3-one (6) from 3.** A mixture of 20 mL of 100% $H_2SO_4$, 10.6 g (0.049 mol) of HgO, and 12.0 g (0.048 mol) of $CF_3CH_2CCl_2CH_2CF_3$ was shaken periodically over 45 min, during which time a thick, nearly white paste resulted. A exotherm also occurred after ca. 10 min and subsided after about 0.5 h. The cooled reaction mixture was added to 75 g of ice and 25 mL of concd HCl. The lower liquid phase was separated and the aqueous layer was extracted with 3 × 35 mL of ether. The combined organic extracts (including the original organic layer) were washed with 10 mL of water, dried ($Na_2SO_4$), and distilled; 5.3 g (56% yield) of 97% pure $CF_3CH_2C(O)CH_2CF_3$ was obtained (bp: 122−123 °C). $^1$H NMR: $\delta$ 3.4 (q, $J$ = 10.2 Hz) ppm. $^{19}$F NMR: $\delta$ −63.0 (t, $J$ = 10.2 Hz) ppm. IR: 1746 (C=O) cm$^{-1}$. MS: 194 (3.4), 111 (100), 91 (17.5), 83 (21.8), 69 (11.9). Anal. Calcd for $C_5H_4F_6O$: C, 30.94; H, 2.08. Found: C, 31.03; H, 2.02.

**1,1,1,5,5,5-Hexafluoropentan-3-ol (7).** Sodium borohydride (0.8 g) was added to 15 mL of water at 0 °C (ice bath). After the $NaBH_4$ had dissolved, 9.7 g of $CF_3CH_2C(O)CH_2CF_3$ was added, which froze. The ice bath was removed until the mixture was warm enough to melt the ketone, and the ice bath cooling was resumed. The reaction was quenched after 1 h with the addition of 5 mL of 2 N HCl and 10 mL of brine. The lower layer (8.9 g) consisted of 95% pure $CF_3CH_2CH(OH)CH_2CF_3$ (91% yield). Distillation increased the purity to 97%. Bp: 65 °C at 95 mmHg. $^1$H NMR: $\delta$ 4.4 (pentet, 1H), 2.9 (s, 1H), 2.4 (m, 4H) ppm. $^{19}$F NMR: $\delta$ −64.2 (t, J = 10 Hz) ppm. FT-IR: 3415 (OH), 1264, 1154 cm$^{-1}$. MS: 113 (64.8), 111 (18.6), 109 (10.8), 93 (91.4), 91 (14.2), 69 (16.5), 65 (100), 64 (33.8), 49 (28.1), 29 (25.8). Anal. Calcd for $C_5H_6F_6O$: C, 30.63; H, 3.08. Found: C, 30.61; H, 3.11.

**3-Methoxy-1,1,1,5,5,5-hexafluoropent-2-ene (9).** A 21.1 g (0.12 mol) sample of allene **10** was added to 20 mL of 0.5 N $NaOCH_3$ in methanol (8 mol % relative to allene) over 1 h with water bath cooling, to keep the reaction temperature at 10−20 °C. Stirring was continued for 15 min and the mixture was poured into 80 mL of cold water. The lower layer was separated and the aqueous portion extracted with 20 mL of $CH_2Cl_2$. The combined organic layers were washed with 5 mL of brine, dried ($Na_2SO_4$), and distilled to give 21.9 g (88% yield) of $CF_3CH{=}C(OCH_3)CH_2CF_3$. Bp: 110−111 °C. IR: 1672 cm$^{-1}$. Major MS fragments: 208 (75.9), 189 (30.2), 158 (31.6), 125 (60.5), 111 (82.4), 91 (100), 31 (91.2). $^1$H NMR: $\delta$ 4.95 (q, 1 H, $J$ = 7.5 Hz), 3.65 (s, 3 H), 3.18 (q, 2 H, $J$ = 9.8 Hz) ppm. $^{19}$F NMR: $\delta$ −54.4 (d, 3 F), −63.9 (t, 3 F) ppm. Anal. Calcd for $C_6H_6F_6O$: C, 34.61; H, 2.91. Found: C, 34.59; H, 2.85.

**Preparation of 6 from Methyl Vinyl Ether 9.** Vinyl ether **9** (21.3 g, 102 mmol) was added to 20 mL (36 g) of concd $H_2SO_4$ at 15−20 °C over 15 min. Stirring was continued for 10 min and the reaction mixture poured into 100 mL of cold water. The product was extracted with 2 × 40 mL of ether. The combined extracts were washed with brine, dried ($Na_2SO_4$), and distilled to give 15.3 g (77% yield) of **6**. Bp: 122−123 °C.

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