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Electrophilic addition reactions of 1,1-difluoro-2,2-diphenylthioethylene

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Abstract

Electrophiles have been shown to add to $F_2C{=}C(SPh)_2$ at the difluoromethylene carbon, indicating that sulfur is better able to stabilize a positive charge than fluorine.

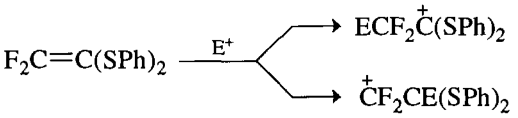
Introduction

A strategy commonly employed in the synthesis of fluorinated organic compounds is the use of fluorinated building blocks. Examples of small molecules that already have C—F bonds that have been used in this manner include derivatives of trifluoroacetic acid [1], dibromodifluoromethane [2] and fluorodichloromethane [3]. In this work, we sought to introduce CF_2 groups into a two-carbon backbone starting with CF_3CHO. Condensation with thiophenol followed by elimination of HF gives rise to the title compound, $F_2C{=}C(SPh)_2$ [4]. Nucleophiles, such as RLi, have been shown to react with 1,1-difluoro-2,2-diphenylthioethylene by an addition–elimination sequence to give rise to 1-alkyl-1-fluoro-2,2-diphenylthioethylene [4, 5]. This is a synthetically useful reaction because monofluorocarboxylic acids are formed upon hydrolysis as shown in eqn. (1).

$$F_2C{=}C(SPh)_2 \xrightarrow{Bu^nLi} Bu^nCF{=}C(SPh)_2 \xrightarrow{H_3O^+} Bu^nCHFCO_2H \quad (1)$$

Electrophilic additions to 1,1-difluoro-olefins generally proceed in such a manner that the intermediate has the positive charge on the carbon bearing the fluorines [6]. It is the π-donor ability of fluorine that allows this orientation for the addition. Even in the case of $Cl_2C{=}CF_2$, where there are π-donors on both carbons, the addition occurs in the direction that results in positive character residing at the carbon bearing the fluorines [7]. Destabilization of the carbocation on the carbon β to the fluorines through a σ-inductive effect is also a contributing factor [8].

In $F_2C{=}C(SPh)_2$, a competition arises. Addition of the electrophile to the carbon bearing fluorine would result in a species stabilized by α-sulfur, but destabilized by β-fluorine as shown in Scheme 1. However, addition to the carbon bearing sulfur would result in a carbocation stabilized by the π-donating ability of fluorine. To determine the outcome of this competition in regiochemistry, we have investigated the reaction of the title fluorinated ketene thioacetal with electrophiles.



Scheme 1.

Results and discussion

Benzhydryl cation, generated from benzhydryl chloride and BCl_3, provides an unstable adduct in the presence of 1,1-difluoro-2,2-diphenylthioethylene. Upon hydrolysis, 3,3-diphenyl-2,2-difluoropropanoic acid is formed as shown in eqn. (2).

$$Ph_2CHCl + F_2C{=}C(SPh)_2 \xrightarrow[H_3O^+,\ HgCl_2]{then} Ph_2CHCF_2CO_2H \quad (2)$$

The α,α-difluoroacid was hygroscopic and could not be obtained analytically pure. For analysis, the acid was treated with thionyl chloride followed by dimethyl amine to form the corresponding amide. The overall yield was 55%.

Although this reaction results in the formation of a difluoroacetic acid, we were unable to extend the reaction to other electrophiles. t-Butyl chloride, trityl

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chloride and benzyl chloride all failed to react with the fluorinated ketene thioacetal. Further, there is no protonation of $F_2C{=}C(SPh)_2$ with HCl, H_2SO_4 or HBF_4.

Addition of the electrophile bromine to $F_2C{=}C(SPh)_2$ in a nonprotic solvent rapidly generated the dibromide. When the reaction was carried out in a protic solvent, the latter could compete with bromide ion for the positively charged intermediate. The addition of bromine to $F_2C{=}C(SPh)_2$ in methanol produced two products. One was the dibromide and the other was the methoxy bromo derivative. Both derivatives could be further oxidized by excess bromine. Spectral data indicate that the product collected was methyl α-bromodifluoroacetate, which indicates that the methoxy group is introduced exclusively at the diphenylthio carbon. The methanol attacks the carbon atom with the more pronounced carbocation character. The reaction is shown in eqn. (3). This result leads to the conclusion that the sulfur has stronger ability to stabilize the carbocation than fluorine, in accord with the σ^+ value for sulfur ($SCH_3 = -0.604$) and for fluorine ($F = -0.073$) [9].

$$F_2C{=}C(SPh)_2 + Br_2 \xrightarrow{CH_3OH} [BrCF_2C(OCH_3)(SPh)_2] \xrightarrow{Br_2} BrCF_2CO_2CH_3 \qquad (3)$$

Experimental

General

^{1}H and ^{13}C NMR spectra were obtained on a GE GN-300 NMR spectrometer. Chemical shifts are reported in ppm downfield relative to internal TMS with $CDCl_3$ as the solvent. ^{19}F NMR spectra were obtained on a Bruker AR-100 spectrometer operating at 95.52 Hz. Spectra were obtained in $CDCl_3$ with chemical shifts reported in ppm relative to external $CFCl_3$. Negative chemical shifts indicate that the resonances are upfield relative to $CFCl_3$. Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. The microanalysis was undertaken by Atlantic Microlab, Inc., Norcross, GA.

Preparation of N,N-*dimethyl-3,3-diphenyl-2,2-difluoropropanamide*

To a CH_2Cl_2 solution (10 ml) containing benzhydryl chloride (0.64 ml, 3.6 mmol) was injected 1.0 M BCl_3 (4.0 ml, 3.0 mmol) in CH_2Cl_2. After stirring the solution at room temperature for 15 min, $F_2C{=}C(SPh)_2$ (1.0 g, 3.6 mmol) in CH_2Cl_2 (2 ml) was introduced. The reaction mixture was stirred for 3 h, then H_2O (10 ml) was added dropwise and stirred for 10 min. $HgCl_2$ (2.0, 7.6 mmol) was added to the reaction mixture which was stirred for 6 h. The hydrolysis generated 3,3-diphenyl-2,2-difluoropropanoic acid and PhSH which was air-oxidized to PhS–SPh. The product mixture was extracted with pentane (3×120 ml), dried with $MgSO_4$ and the solvent removed by rotary evaporation. To the crude products in CH_2Cl_2 (20 ml) was added Et_3N (1.5 ml, 11 mmol) and Et–SH (0.50 ml, 6.8 mmol). The reaction mixture was stirred overnight. The reaction was traced by TLC which showed that there was no PhS–SPh present. The product was extracted with hexanes (200 ml) and washed successively with 1 N HCl (2×100 ml), 1 N NaOH (2×100 ml), saturated NaCl (2×100 ml) and H_2O (2×100 ml). The organic phase was dried with $MgSO_4$, filtered and the solvent evaporated. Crude acid (0.78 g, 83%) was collected. The crude acid (0.78 g, 3.0 mmol) reacted with $SOCl_2$ (5.0 ml, 69 mmol) and the mixture refluxed for 2 h. The excess $SOCl_2$ was removed by rotary evaporation. The mixture was dissolved in dry THF solution (20 ml) and added dropwise to a THF (10 ml) solution containing dimethylamine (3 ml). After stirring for 1 h, the product was extracted with CH_2Cl_2 (100 ml), washed successively with 1 M HCl (2×100 ml), saturated NaCl (2×100 ml) and H_2O (2× 100 ml), dried with $MgSO_4$, filtered and the solvent removed by rotary evaporation to obtain the crude amide (0.59 g, 2.0 mmol). The product was recrystallized from petroleum ether. The overall yield was 55%; m.p. 66–67 °C. ^{1}H NMR ($CDCl_3$) δ: 2.90 (s, 3H); 3.05 (s, 3H); 5.03 (t, $J_{HF} = 17.5$ Hz, 1H); 7.24–7.43 (m, 10H) ppm. ^{19}F NMR ($CFCl_3$) δ: −105 (d, $J_{HF} = 17.5$ Hz) ppm. Analysis: Calc. for $C_{17}H_{17}F_2NO$: C, 70.57; H, 5.92; N, 4.84%. Found: C, 70.67; H, 5.89; N, 4.83%.

Preparation of methyl bromodifluoroacetate

Bromine (5.0 ml, 97 mmol) was dissolved in methanol (30 ml) and then transferred to a dropping funnel. The bromine solution was added dropwise to a methanol (30 ml) solution containing $F_2C{=}C(SPh)_2$ (5.0 g, 18 mmol) at room temperature. When the addition of bromine was complete, the mixture was refluxed overnight with stirring. The crude products were directly distilled out of the flask. The products were extracted with methylene chloride (200 ml), washed with aqueous sodium thiosulfate solution (2×100 ml) and H_2O (150 ml), dried with $MgSO_4$ and filtered. The product was purified by simple distillation. The yield was 30–35%; b.p. 94–96 °C (lit. value [10] b.p. 96 °C). ^{1}H NMR ($CDCl_3$) δ: 3.98 ppm. ^{13}C NMR ($CDCl_3$) δ: 54.46, 108.48 (t, $J_{CF} = 314.98$ Hz); 160.09 (t, $^{3}J_{CF} = 31.74$ Hz) ppm. ^{19}F NMR ($CFCl_3$) δ: −61.5 ppm. IR (neat) (cm^{-1}): 1787; 1430; 1306; 1174; 1124; 980; 913.

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