Reactions of tetrafluoroethene oligomers. Part 16.[1] The synthesis and reactions of perfluoro[2,3-dimethyl-2-(3-methylpentan-3-yl)]-2H-azirine: a source of 2,3-bis(trifluoromethyl)aziridine derivatives

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The reaction of perfluoro(4-ethyl-3,4-dimethylhex-2-ene) (TFE pentamer) with sodium azide in acetonitrile afforded perfluoro[2,3-dimethyl-2-(3-methylpentan-3-yl)]-2H-azirine as a stable distillable liquid. The azirine reacted slowly with nucleophiles to give a series of substituted 2,3-bis-(trifluoromethyl)aziridines. A rationale of this somewhat unexpected reaction is suggested.

Introduction

Although the chemistry of hydrocarbon 2H-azirines is well known and the subject has been reviewed,[2] there are few reports of the preparation and reactions of corresponding fluoro-carbon analogues. Their chemistry has been little studied mainly due to their high reactivity towards nucleophiles including moist air. The first syntheses of fluorinated azirines were published by Knunyants[3] and almost concurrently by Krespan[4] and Banks.[5] These authors showed that perfluoropropene would react with azide ion to yield a mixture of compounds one of which was perfluoro(2-methyl-2H-azirine) **1** which rapidly isomerises in the presence of fluoride ion to the more stable isomer perfluoro(3-methyl-2H-azirine) **2**. The original work of Knunyants turned out to be incomplete and slightly inaccurate but the results of Krespan and Banks were in agreement. Subsequently Krespan[6] and Banks[7] reported further studies in this area but only the 2H-azirine **3** from 1-methoxy-2-(trifluoro-methyl)-1,3,3,3-tetrafluoropropene was reported as a new derivative in this class, again as a relatively unstable compound which rearranged on heating. These results are summarised in Scheme 1. Since this time there appears to have been no liter-ature reports of perfluoroazirines. Liebman[8] has suggested, on the basis of MO calculations, that unstable structures may be stabilised by substitution with bulky fluoroalkyl groups. We have indeed shown this to be the case *inter alia* of an ethanolide (α-lactone)[9] and a diazoalkane.[10] We were thus interested to see if such substitution would have the same effect on azirines and if it were successful to study some of their chemistry.

Results and discussion

Tetrafluoroethene pentamer **4** was treated with sodium azide at room temperature and gave, after a standard work-up procedure, a colourless clear liquid in high yield. Chromatographic analysis showed this to be essentially a single component although the IR spectrum of the crude material did show a band at 2135 cm^{-1} characteristic of an azide in addition to a strong band at 1780 cm^{-1} from the major component of *ca.* 1785 cm^{-1} for **2**.[4] The product, unlike those reported earlier from hexafluoropropene, could be distilled without decomposition even on a 150 g scale. The IR spectrum of the pure product showed only the band at 1780 cm^{-1}. The ^{19}F NMR spectrum showed a series of bands characteristic for the perfluoro-3-methylpentyl group which are virtually identical for all compounds we have prepared from **4**. In addition there were two resonances for trifluoromethyl groups but no band for the olefinic fluorine atom found in **4**. The mass spectrum and elemental analysis confirmed the structure as being perfluoro-[2,3-dimethyl-2-(3-methylpentan-3-yl)]-2H-azirine **5**. We have referred to this compound in an earlier paper and have described its pyrolysis to E/Z-2-cyanoperfluoro(3-methylpent-2-ene) but have not hitherto described its synthesis and chemical reactions.[11]

We next investigated the reactions of **5** with nucleophiles, and it was immediately clear that the compound was much more stable than the previously reported polyfluoroazirines. We found no evidence on prolonged standing for any decomposition or hydrolysis, indeed heating with water alone for several days had no effect on **5**. The reduction of hydrocarbon azirines with LAH is well documented as a means of preparing aziridines[12] and we therefore examined this reaction with **5**. The azirine **5** was treated with an excess of LAH to give on work up a crystalline solid, shown by TLC to be a single component. ^{1}H NMR spectroscopy showed two bands in the ratio of 1:2 at δ 4.8 and 3.1 respectively. The band at δ 4.8 was exchangeable with D$_2$O and we assign this as an NH group. The band at 3.1 was strongly coupled to give a very complex multiplet which
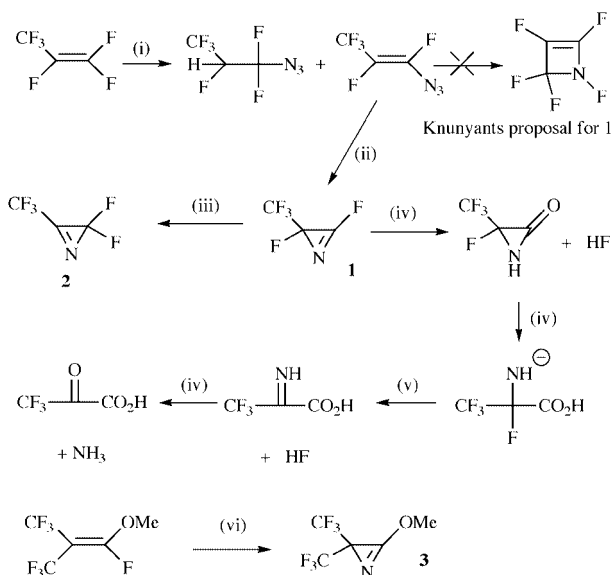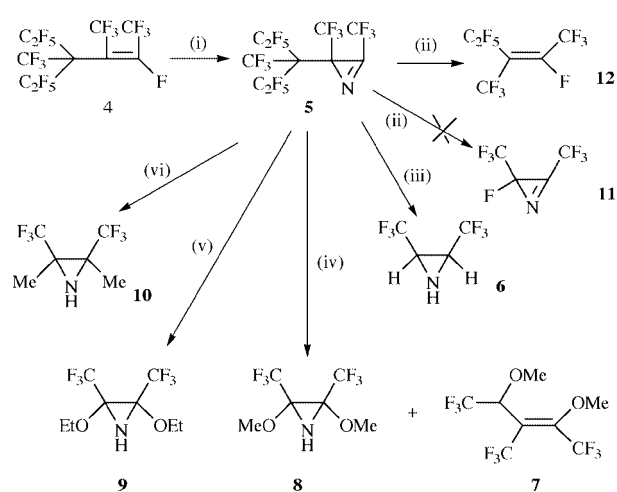

Scheme 1 *Reagents and conditions*: (i) Bu$_4$N$_3$; (ii) heat; (iii) HF; (iv) H$_2$O; (v) −HF; (vi) NaN$_3$.

could not be analysed. The ^{19}F NMR spectrum was totally unexpected: it showed a single resonance at δ -65.8 as a strongly coupled multiplet which we can assign to two identical trifluoromethyl groups. Since we cannot analyse the spectrum we cannot distinguish between them both being *cis* or both *trans* on the basis of any coupling constant values. Literature precedent [12] in the hydrocarbon field suggests that the reduction should give the *cis*-compound, hence we tentatively assign the two groups being in the *cis* arrangement. The expected bands of the perfluoro(3-methylpentyl) function had completely disappeared (see below). The IR spectrum showed that there was no absorption at 1780 cm^{-1} indicating that the azirine ring was absent. The mass spectrum and elemental analysis were consistent with the compound being 2,3-bis(trifluoromethyl)aziridine **6**.

We next reacted **5** with an excess of sodium methoxide in methanol and Arcton 113 (CF$_2$ClCFCl$_2$). The product, a mixture of two components, could be separated by preparative GLC to yield 2,3-dimethoxyperfluoro(3-methylpent-2-ene) **7**, a known compound obtained from the reaction of TFE trimer **12** and sodium methoxide,[13] and a white crystalline solid **8**. The ^{1}H NMR spectrum of the latter showed bands for two identical methoxy groups and a band for the NH function; the ^{19}F spectrum again showed only one signal for CF$_3$ groups as a sharp singlet indicating that the two groups were in the same magnetic environment. The mass spectral and elemental analysis data were consistent with the structure being 2,3-dimethoxy-2,3-bis(trifluoromethyl)aziridine **8**. In a similar reaction sodium ethoxide afforded the corresponding 2,3-diethoxy-2,3-bis(trifluoromethyl)aziridine **9**. In this case none of the corresponding 2,3-diethoxyperfluoro(3-methylpent-2-ene) was isolated. Reaction of **5** with methylmagnesium iodide afforded a white solid which showed bands in its ^{1}H NMR spectrum at δ 4.6 and 1.3 in the ratio 1:6, the signal at 4.6 exchanged with D$_2$O. We assign these bands to an NH group and two methyl groups respectively. The ^{19}F NMR spectrum again showed only a single sharp band for CF$_3$ groups. These data and the mass spectral and elemental analysis data confirm the compound as 2,3-dimethyl-2,3-bis(trifluoromethyl)aziridine **10**. With the reaction pathway of the azirine **5** now clearly established we hoped that it would provide a simple route to the as yet unknown 3-fluorobis(trifluoromethyl)-2H-azirine **11** by reaction of **5** with fluoride ion. The azirine **5** was heated with a suspension of potassium fluoride in acetonitrile in a Carius tube at 100 °C for 12 h, the tube was carefully opened and the crude fluorocarbon layer was analysed by GLC ^{1}H and ^{19}F NMR spectroscopy and GC-MS, all of which indicated that the major product (>95%) of the mixture was TFE trimer **12**, clearly formed from the elimination of the perfluoro(3-methylpentyl) group from **5**. The minor products were breakdown low molecular weight materials but no evidence for the formation of the hoped for azirine **11** was found. There was no evidence for the polymer formation noted by Krespan [4] in his studies of **1** and **2**. This result, although not giving the compound we hoped for, still represents a very simple route to TFE trimer **12** which is very difficult to obtain by other methods. This is quite important since **12** occurs only to a very small extent in the oligomerisation process. We found that amines caused extensive decomposition when reacted with **5** and azide ion did not react a second time. These reactions are summarised in Scheme 2.

The loss of the perfluoro(3-methylpentyl) group was slightly surprising in this case since it has not been observed previously in nucleophile attack on TFE pentamer **4** and its derivatives. Such a reaction was observed in the addition 2-pentafluoroethyl-3,3,4,4,4-pentafluoro-2-trifluoromethyldiazabutane to acrylate esters when pyrazole derivatives free of fluorine were obtained.[14] We postulated then that this was due the perfluoro(3-methylpentyl) group acting either as an excellent leaving group in its own right or equally well as perfluoro(2-methylpent-2-ene) (TFE trimer) **12** and fluoride ion both of

Scheme 2 *Reagents and conditions*: (i) N$_3^-$; (ii) F$^-$; (iii) LAH; (iv) MeO$^-$; (v) EtO$^-$; (vi) MeMgI.

which would be favourable processes. In this reaction there is a further driving force for the elimination to form the observed pyrazoles which have some degree of aromatic stabilisation. The proposed mechanism is shown graphically in Scheme 3.
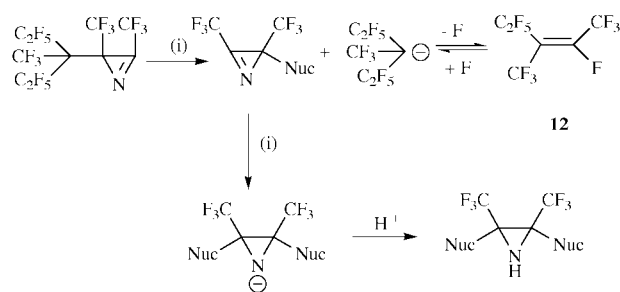
Scheme 3 *Reagents and conditions*: (i) Nucleophile = H$^-$, RO$^-$, Me$^-$ *etc.*

Thus, this study presents a new and simple route to a relatively unknown but potentially useful series of fluorocarbon derivatives. Since there are a number of bioactive molecules which contain such groups in the hydrocarbon series *e.g.* azirinomycin and *R*-dysidazirine and given that the introduction of fluorine often enhances bioactivity, the types of reaction we have described may lead to novel compounds of potential pharmaceutical use.

Experimental

^{1}H NMR spectra (300 MHz) were measured on a Bruker AC 300 NMR spectrometer unless stated otherwise. ^{19}F NMR spectra were carried out either on a JEOL NMR spectrometer, type FX 90 Q (84.26 MHz) or on a Bruker AC 300 NMR spectrometer (282.4 MHz); tetramethylsilane and fluorotrichloromethane were used as internal references. For the characterisation of the signals the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, "quin" = pseudo quintet *etc.* *J* values are given in Hz. The mass spectra (CI-MS/EI-MS) were measured on a VG-Prospec-triple focusing mass spectrometer. For GC-MS analysis, a Carlo Erba, 8000 series GC was used with a 50 metre column, BPX 5 (helium carrier gas, 70 eV, electron impact).

Thin layer chromatography was performed on TLC silica gel 60 F$_{254}$ plastic sheets pre-coated with a layer thickness of 0.2 mm from Merck, Art. 5735. Gas chromatographic analysis was carried out using a Philips PYE Unicam, Series 304 chromato-

graph with a 50 metre CD-SIL-CB 19 column. The data were registered by a JCL 600 chromatography data system.

Preparation of perfluoro[2,3-dimethyl-2-(3-methylpentan-3-yl)]-2*H*-azirine 5

Perfluoro(4-ethyl-3,4-dimethylhex-2-ene) (TFE pentamer) (150 g, 0.3 mol) was added dropwise to a well stirred suspension of dry sodium azide (36 g, 0.46 mol) in Arcton 113 (150 cm³) and dry acetonitrile (80 cm³) containing 18-crown-6 (0.01 g). When the addition was complete the mixture was stirred for a further 20 h. The fluorocarbon layer was separated and the Arcton was distilled off. The ^{19}F NMR spectrum of the residue was taken and the crude product was distilled *in vacuo* using a 10 cm Vigreux column to yield perfluoro[2,3-dimethyl-2-(3-methylpentan-3-yl)]-2*H*-azirine 5 (105 g, 71%) bp 42 °C at 15 mmHg (Found: C, 24.1; N, 2.6; F, 72.6%. $C_{10}F_{19}N$ requires C, 24.3; N, 2.8; F, 72.9%); δ_F (CDCl₃) −57.9 (m, 3F, CF₃,), −62.4 (m, 3F, CF₃), −64.9 (m, 3F, CF₃), −78.3 (m, 6F, CF₃), −102.4 to −103.9 (m, 4F, CF₂); IR 1780 cm^{-1} (C=N); MS *m/z* 476 [M − F], 395 [M − C_2F_4], 376 [M − C_2F_5].

Reactions of perfluoro[2,3-dimethyl-2-(3-methylpentan-3-yl)]-2*H*-azirine 5

(a) With lithium aluminium hydride (LAH). The azirine 5 (5.0 g, 0.01 mol) in dry ether (10 cm³) was added to a stirred suspension of LAH (1.0 g, 0.014 mol) in dry ether (100 cm³) at 5 °C. After the addition was complete the mixture was stirred for 6 h at 18 °C. 10% Aqueous sodium hydroxide (5 cm³) was added and the resulting solids filtered off. The ether layer was evaporated to leave a pale yellow solid which was purified by sublimation *in vacuo* (50 °C at 10 mmHg) to yield 2,3-bis(trifluoromethyl)aziridine 6 (3.2 g), mp 75–77 °C as white crystals (Found: C, 26.7; H, 1.6; N, 7.7%. $C_4H_3F_6N$ requires C, 26.8; H, 1.7; N, 7.8%); δ_H (CDCl₃) 4.8 (br s, 1H, D₂O exchangeable, NH), 3.1 (m, 2H, CH); δ_F (CDCl₃) −65.8 (m, CF₃); MS *m/z* 179 [M]⁺, 110 [M − CF₃]⁺, 90 [M − CF₃ − HF]⁺.

(b) With sodium methoxide. Sodium methoxide (2.2 g, 0.04 mol) in methanol (5 cm³) was added dropwise to a solution of 5 (10 g, 0.02 mol) in Arcton 113 (30 cm³) at 18 °C. The mixture was stirred for 12 h and was then washed with 2 M HCl (10 cm³) and water (2 × 10 cm³) and dried (MgSO₄). Evaporation of the Arcton afforded a liquid (8.9 g) shown by analytical GLC to contain two components. Separation of a portion (1 g) of the mixture by preparative GLC (tetracyanoethylated pentaerythritol–Celite 1:3, 130 °C, N₂, 10 dm³ h^{-1}) gave (i) 2,4-dimethoxyperfluoro(3-methylpent-2-ene) 7 (0.2 g) identical to an authentic sample[13] and (ii) 2,3-dimethoxy-2,3-bis(trifluoromethyl)aziridine 8 (0.6 g), mp 58–59 °C as a white crystalline solid (Found: C, 30.1; H, 2.6; N, 5.7%. $C_8H_7F_6NO_2$ C, 30.1; H, 2.9; N, 5.9%); δ_H (CDCl₃) 4.5 (br s, 1H, exchangeable with D₂O, NH), 3.48 (s, 6H, OCH₃); δ_F (CDCl₃) −69.4 (s, CF₃); MS *m/z* 224 [M − OMe]⁺, 170 [M − CF₃]⁺.

(c) With sodium ethoxide. In the same way as above 5 (10 g, 0.02 mol) was reacted with sodium ethoxide (2.8 g, 0.04 mol) in ethanol (5 cm³) to give after distillation *in vacuo* (68 °C at 0.5 mmHg) 2,3-diethoxy-2,3-bis(trifluoromethyl)aziridine 9 (6.8 g) mp 51–52 °C (Found: C, 36.2; H, 4.4; N, 5.4%. $C_8H_{11}F_6N$ requires C, 36.0; H, 4.1; N, 5.3%); δ_H (CDCl₃) 4.6 (br s, 1H, exchangeable with D₂O, NH), 3.85 (q, 4H $^1J_{HH}$ 7, CH₂), 1.2 (t, 6H, $^1J_{HH}$ 7, CH₃); δ_F (CDCl₃) −69.4 (s, CF₃); MS *m/z* 198 [M − CF₃]⁺.

(d) With methylmagnesium iodide. Methylmagnesium iodide (from methyl iodide 6.3 g and magnesium 1.1 g) in dry ether (50 cm³) was added dropwise from a pressure equalised dropping funnel in an atmosphere of nitrogen to a solution of 5 (10 g) in ether (25 cm³) at 0 °C. When the addition was complete the mixture was stirred at 18 °C for 20 h. Saturated ammonium chloride solution (50 cm³) was added, the ether layer separated and combined with the ether extracts (2 × 25 cm³) of the aqueous layer. The ether layer was dried (MgSO₄) and the ether evaporated to leave a pale yellow solid which was purified by sublimation *in vacuo* (10 mmHg) to give as white crystals 2,3-dimethyl-2,3-bis(trifluoromethyl)aziridine 10 (7.5 g) mp 61–63 °C (Found: C, 34.6; H, 3.2; N, 6.9%. $C_6H_7F_6N$ requires C, 34.8; H, 3.4; N, 6.8%); δ_H (CDCl₃) 4.7 (br s, 1H, NH), 1.4 (s, 6H, CH₃); δ_F (CDCl₃) −67.6 (s, CF₃); MS *m/z* 192 [M − CH₃], 138 [M − CF₃]. Found mass 207.04831. Required mass ($C_6H_7F_6N$) 207.04827.

(e) With fluoride ion. The azirine 5 (1.5 g), spray dried potassium fluoride (0.5 g) in acetonitrile (5 cm³) and 18-crown-6 (0.01 g) were heated together in a sealed Carius tube at 100 °C for 20 h. The tube was frozen in liquid air, opened and attached to a vacuum line, the volatile material was transferred to a separate tube in the usual way and the clear liquid obtained was shown to be almost pure perfluoro(3-methylpent-2-ene) 12 (0.7 g, 70%) identical in all respects to an authentic sample.

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