Novel Preparation of 3-Alkyl-5-hydroxy-5-per(poly)fluoroalkyl-4,5-dihydroisoxazoles

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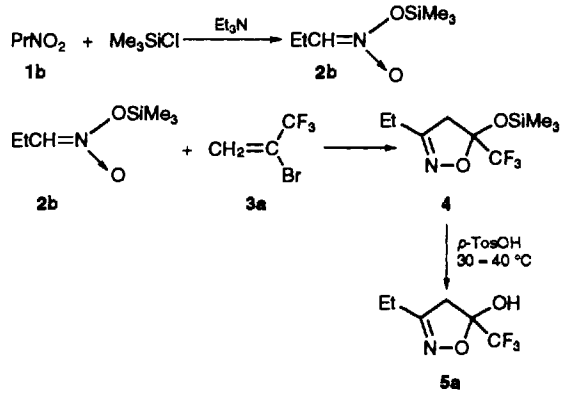
3-Alkyl-5-hydroxy-5-per(poly)fluoroalkyl-4,5-dihydroisoxazoles have been synthesized by a 1,3-dipolar cycloaddition of trimethylsilyl nitronates to 1-bromo-1-per(poly)fluoroalkylethene *via* a one-pot or two-step reaction. The reaction was regiospecific and an intermediate containing the trimethylsiloxy group has been isolated.

In recent years, much attention has been paid to the development of new methodologies for the synthesis of various fluorine-containing heterocyclic compounds, which are now widely recognized as important materials utilized in the medicinal and agricultural fields.[1–3] One of the methods used in such syntheses is the cycloaddition of 1,3-dipoles to carbon–carbon multiple bonds.[4] However, papers concerning the cycloaddition of 1,3-dipoles to fluorine-containing alkenes are rare. Gallucci *et al.* reported the synthesis of 5-perfluoroalkyl-4,5-dihydroisoxazoles and 5-perfluoroalkylisoxazoles by the 1,3-dipolar cycloaddition of nitrile oxides to perfluoroalkylated alkenes and alkynes.[5] Herein, we report the synthesis of 4,5-dihydroisoxazoles by the 1,3-dipolar cycloaddition of readily available trimethylsilyl nitronates[6,7] to 1-bromo-1-per(poly)-fluoroalkylethenes.

Results and Discussion

Trimethylsilyl nitronates **2a** and **2b** were readily prepared from nitroethane **1a** and 1-nitropropane **1b**, respectively (Scheme 1).[6]



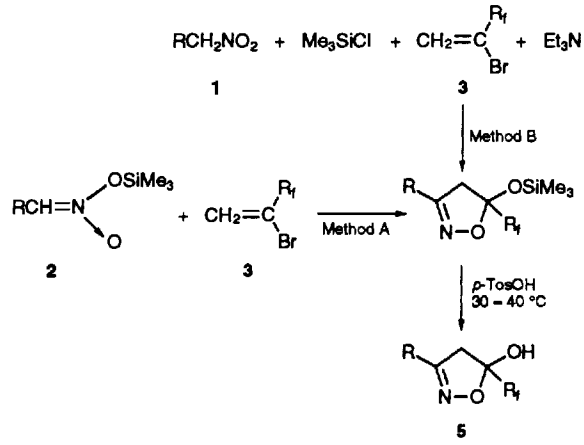
Scheme 1

1-Bromo-1-per(poly)fluoroalkylethenes **3** were made according to known methods.[8,9] A mixture of nitronate **2b** (2 equiv.) and 2-bromo-1,1,1-trifluoroprop-2-ene **3a** in benzene, with a small amount of Et_3N as stabilizer,[6] was stirred at 30–40 °C for 2 days and 3-ethyl-5-trifluoromethyl-5-trimethylsiloxy-4,5-dihydroisoxazole **4** was obtained in 78% isolated yield by flash chromatography (silica gel, light petroleum b.p. 60–90 °C as eluent) as the only product.

Gallucci *et al.* reported that two isomeric perfluoroalkylated 4,5-dihydroisoxazoles were obtained from nitrile oxides with 1-bromo-1-perfluoroalkylethene.[5] However, in our case, the reaction was regiospecific and only one isomer was obtained in which the substituents were at the 5-position of the 4,5-dihydroisoxazole ring, while the other isomer (substituted at the 4-position) could not be detected.

Compound **4** was stable at room temperature for several days. On treatment with a catalytic amount of *p*-TosOH in benzene at 40–50 °C, the trimethylsiloxy group was eliminated and 3-ethyl-5-hydroxy-5-trifluoromethyl-4,5-dihydroisoxazole **5b** was obtained in nearly quantitative yield. Compound **5b** was isolated as light yellow needles stable at room temperature and could be purified by recrystallization from chloroform or by sublimation.

Further investigation showed that this two-step reaction: cycloaddition and elimination, could be simplified. That is, the crude product **4** was directly used to eliminate the trimethylsiloxy group with a catalytic amount of *p*-TosOH, giving compound **5b** in an 82% isolated yield from **3a**. Later, it was found that 5-hydroxy-4,5-dihydroisoxazole **5b** could be obtained directly from 1-nitropropane **1b** by a one-pot reaction. Thus, during the trimethylsilylation of 1-nitropropane **1b**, 2-bromo-1,1,1-trifluoroprop-2-ene **3a** was added to trap the intermediate formed and to give the crude product **4** which on treatment with a catalytic amount of toluene-*p*-sulfonic acid gave compound **5b** in 64% overall yield (Method B, Scheme 2).



Scheme 2

The reaction was widened to other trimethylsilyl nitronates **2** or nitroalkanes **1** and other 1-bromo-1-per(poly)fluoroalkyl-ethenes **3** either in a two-step (Method A) or in a one-pot (Method B) reaction. The results are summarized in Table 1. As shown in Table 1, the nature of R and the length of the R_f chain have little influence on the yield of **5**. The nature of the halogen atom at the end of R_f chain did not affect the reaction either.

Table 1 Synthesis of 3-alkyl-5-hydroxy-5-per(poly)fluoroalkyl-4,5-dihydroisoxazoles **3**

Compound 5	R	R_f	Starting Materials: 1 or 2	3	Method	Yield (%)[a]
5a	Me	CF_3	**1a**	**3a**	B	76
5b	Et	CF_3	**2b**	**3a**	A	82
5b	Et	CF_3	**1b**	**3a**	B	64
5c	Me	C_2F_4Br	**1a**	**3b**	B	65
5d	Et	C_2F_4Br	**1b**	**3b**	B	62
5e	Me	C_4F_8Cl	**2a**	**3c**	A	72
5e	Me	C_4F_7Cl	**1a**	**3c**	B	50
5f	Et	C_4F_8Cl	**1b**	**3c**	B	60
5g	Me	$C_6F_{12}Cl$	**1a**	**3d**	B	64
5g	Me	$C_6F_{12}Cl$	**2a**	**3d**	A	78
5h	Et	$C_6F_{12}Cl$	**1b**	**3d**	B	77

[a] Isolated yield based on **3**.

Nitroethane and 1-nitroethane were suitable substrates, however, nitromethane failed to react with 2-bromo-1,1,1-trifluoroprop-2-ene **3a**, either by Method A or Method B, and a complicated mixture of products was obtained.[6]

In the NMR spectra of 4,5-dihydroisoxazoles **5**, the CH_2 group on the ring always gives an AB spectrum with chemical shifts appearing at δ 3.2–3.6, J_{AB} 18–23 Hz. It is interesting to note that the CF_2 group on the asymmetric carbon C-5 gives an AB spectrum (J_{AB} 180 Hz), except for **5a** or **5b**, $R_f = CF_3$ (which is a singlet).

Experimental

IR spectra were recorded on a Shimadzu IR-440 spectrometer as films or KBr plates. ^{19}F NMR spectra were recorded on a Varian-360L (56.4 MHz) spectrometer in $CDCl_3$ or [$^2H_6$]acetone using CF_3CO_2H as external standard. Chemical shifts in ppm were positive for upfield shifts. ^1H NMR spectra were recorded in $CDCl_3$ or [$^2H_6$]acetone on an XL-200 (200 MHz) or a Bruker (300 MHz) spectrometer. Mass spectra were obtained on a Finnigan GC–MS–4021 or Finnigan-8430 spectrometer. *J*-Values are given in Hz.

Trimethylsilyl nitronates **2** were prepared from 1-nitroalkanes **1** according to the literature.[6] Trimethylsilyl ethylnitronate **2a**, b.p. 65–67 °C/25 mmHg. Trimethylsilyl propylnitronate **2b**, b.p. 60 °C/15 mmHg.

Cycloaddition of Trimethylsilyl Nitronates **2** *to* 1-*Bromo*-1-*per(poly)fluoroalkylethenes* **3**.—*General procedure.* A mixture of 1-bromo-1-per(poly)fluoroalkylethene **3** (10 mmol), trimethylsilyl nitronate **2** (20 mmol) and Et_3N (0.5 cm^3) in benzene (20 cm^3) was stirred at 30–40 °C for 2 days. The reaction was monitored by ^{19}F NMR. After it was complete, the mixture was poured into water (30 cm^3) and extracted with ethyl acetate (3 × 20 cm^3). The combined extracts were successively washed with dil. HCl (1 mol dm^{-3}; 15 cm^3), water and brine and then dried over Na_2SO_4. After removal of solvent, an oil was obtained. For **2b** and **3a**, the residual oil was purified by flash chromatography (silica gel, petroleum 60–90 °C as eluent) giving pure compound **4**. Otherwise the residue was directly dissolved in benzene (20 cm^3) containing *p*-TosOH (50 mg) and then stirred at 40 °C for 2 h. The reaction was monitored by GC (OV-1). The mixture was then poured into water (20 cm^3), and extracted with ethyl acetate (2 × 20 cm^3). The combined extracts were washed with dil. HCl (1 mol dm^{-3}, 15 cm^3), water and brine and then dried over Na_2SO_4. After removal of solvent, the residue solidified on standing and was recrystallized from $CHCl_3$ to give pure product **5**.

Cycloaddition of Nitroalkanes **1** *with* 1-*Bromo*-1-*per(poly)fluoroalkylethenes* **3** *by a one-pot reaction.*—*General procedure.* A mixture of 1-bromo-1-per(poly)fluoroalkylethene **3** (10 mmol), nitroalkane **1** (20 mmol), triethylamine (20 mmol) and chlorotrimethylsilane (20 mmol) in benzene (50 cm^3) was stirred at 30–40 °C for 2 days. Work-up as described above gave the product **5**.

3-*Ethyl*-5-*trifluoromethyl*-5-*trimethylsiloxy*-4,5-*dihydroisoxazole* **4**. δ_F 5 (s, CF_3); δ_H 3.14 (AB, *J* 22.5, 2 H, cyc-CH_2), 3.0 (q, *J* 10, 2 H, CH_2), 1.19 (t, *J* 10, 3 H, CH_3) and 0.35 (s, 9 H, $SiMe_3$); ν_{max}/cm^{-1} 1640w (C=N), 1220, 1180s (C–F) and 1020s; *m/z* 256 (M^+ + 1, 100%), 186 ($M^+ - CF_3$, 6.01), 166 (M^+ – OTMS, 4.47) and 240 ($M^+ - CH_3$, 16.89) (Found: C, 42.3; H, 6.4; N, 5.5. Calc. for $C_9H_{16}F_3NO_2Si$, C, 42.53; H, 6.27; N, 5.49%).

5-*Hydroxy*-3-*methyl*-5-*trifluoromethyl*-4,5-*dihydroisoxazole* **5a**. δ_F 5 (s, CF_3); δ_H 4.5 (m, 1 H, OH), 3.28 (AB, *J* 18, 2 H, cyc-CH_2) and 2.08 (s, 3 H, CH_3); ν_{max}/cm^{-1} 3500s (OH), 1720m, (C=N), 1200 and 1080s (C–F); *m/z* 169 (M^+, 9.05%), 152 (M^+ – OH, 4.09), 100 ($M^+ - CF_3$, 73.27), 82 ($M^+ - CF_3 - H_2O$, 11.86) and 58 (100) (Found: C, 35.8; H, 3.5; N, 8.3; F, 34.1. Calc. for $C_5H_6F_3NO_2$, C, 35.50; H, 3.55; N, 8.28; F, 33.73%).

3-*Ethyl*-5-*hydroxy*-5-*trifluoromethyl*-4,5-*dihydroisoxazole* **5b**. δ_F 5 (s, CF_3); δ_H 4.6 (m, 1 H, OH), 3.3 (AB, *J* 22.5, 2 H, cyc-CH_2), 2.9 (q, *J* 10, 2 H, CH_2), 1.2 (t, *J* 10 and 3 H, CH_3); ν_{max}/cm^{-1} 3300s (OH), 1680m (C=N), 1150 and 1080s (C–F); *m/z* 183 (M^+, 31.99%), 114 ($M^+ - CF_3$, 22.07) and 86 (100) (Found: M, 183.0480. Calc. for $C_6H_8F_3NO_2$: *M*, 183.0577).

5-(2-*Bromotetrafluoroethyl*)-5-*hydroxy*-3-*methyl*-4,5-*dihydroisoxazole* **5c**. δ_F −16.5 (s, 2 F, CF_2Br) and 40 (AB, *J* 180, 2 F, CF_2); δ_H 4.5 (m, 1 H, OH), 3.6 (AB, *J* 22.5, 2 H, cyc-CH_2) and 2.0 (s, 3 H, CH_3); ν_{max}/cm^{-1} 3400s (OH), 1700m (C=N), 1250 and 1140s (C–F); *m/z* 264 ($M^+ - CH_3$, 0.11%) and 58 (100) [Found: ($M^+ - CH_2 - Br$), 186.0157. Calc. for $C_6H_6BrF_4NO_2$: ($M^+ - CH_2 - Br$), 186.0177].

5-2-*Bromotetrafluoroethyl*)-3-*ethyl*-5-*hydroxy*-4,5-*dihydroisoxazole* **5d**. δ_F −16 (s, 2 F, CF_2Br) and 40 (AB, *J* 180, 2 F, CF_2); δ_H 3.6 (AB, *J* 22.5, 2 H, cyc-CH_2), 3.4 (m, 1 H, OH), 2.9 (q, *J* 10, 2 H, CH_2) and 1.2 (t, *J* 10, 3 H, CH_3); ν_{max}/cm^{-1} 3300s (OH), 1640m (C=N), 1200 and 1140s (C–F); *m/z* 293 (M^+, 7.49%, ^{79}Br), 295 (M^+, 5.55, ^{81}Br), 186 ($M^+ - Br - C_2H_4$, 63.26) and 86 (100) (Found: C, 28.5; H, 2.6; N, 4.6; F, 25.9. Calc. for $C_7H_8BrF_4NO_2$: C, 28.57; H, 2.72; N, 4.76; F, 25.86%).

5-(4-*Chlorooctafluorobutyl*)-5-*hydroxy*-3-*methyl*-4,5-*dihydroisoxazole* **5e**. δ_F −9 (s, 2 F, CF_2Cl), 42 (m, 4 F, 2 × CF_2) and 44 (AB, *J* 180, 2 F, CF_2); δ_H 4.5 (m, 1 H, OH), 3.3 (AB, *J* 22.5, 2 H, cyc-CH_2) and 2.0 (s, 3 H, CH_3); ν_{max}/cm^{-1} 3200s (OH), 1640m (C=N), 1200 and 1140s (C–F); *m/z* 336 (M^+ + 1, 3.14%, ^{35}Cl), 338 (M^+ + 1, 1.30, ^{37}Cl), 317 ($M^+ - H_2O$, 5.89), 100 ($M^+ - C_4F_8Cl$, 100), 85 (26.83) and 69 (CF_3^+, 42.52) (Found: C, 28.5; H, 1.8; N, 4.3; F, 45.4. Calc. for $C_8H_6ClF_8NO_2$: C, 28.61; H, 1.79; N, 4.17; F, 45.3%).

5-(4-*Chlorooctafluorobutyl*)-3-*ethyl*-5-*hydroxy*-4,5-*dihydroisoxazole* **5f**. δ_F −8.3 (s, 2 F, CF_2Cl), 43 (m, 4 F, 2 × CF_2) and 44 (AB, *J* 180, 2 F, CF_2); δ_H 4.2 (m, 1 H, OH), 3.2 (AB, *J* 22.5, 2 H, cyc-CH_2), 3.0 (q, *J* 10, 2 H, CH_2) and 1.2 (t, *J* 10, 3 H, CH_3); ν_{max}/cm^{-1} 3200s (OH), 1640m (C=N), 1200 and 1120s (C–F); *m/z* 350 (M^+ + 1, 12.65%, ^{35}Cl), 352 (M^+ + 1, 2.32, ^{37}Cl), 114 ($M^+ - C_4F_8Cl$, 24.15) and 86 (100) (Found: C, 30.85; H, 2.2; N, 3.7; F, 43.4. Calc. for $C_9H_8ClF_8NO_2$: C, 30.90; H, 2.28; N, 4.00; F, 43.49%).

5-(6-*Chloroperfluorohexyl*)-5-*hydroxy*-3-*methyl*-4,5-*dihydroisoxazole* **5g**. δ_F −10 (s, 2 F, CF_2Cl), 42 (m, 8 F, 4 × CF_2) and 44 (AB, *J* 180, 2 F, CF_2); δ_H 3.3 (AB, *J* 22.5, 2 H, cyc-CH_2), 3.1 (m, 1 H, OH) and 2.0 (s, 3 H, CH_3); ν_{max}/cm^{-1} 3200s

(OH), 1640m (C=N), 1200 and 1140 (s, C–F); m/z 436 ($M^+ + 1$, 93.06%, ^{35}Cl), 438 ($M^+ + 1$, 50.67, ^{37}Cl), 418 ($M^+ - OH$, 54.81, ^{35}Cl), 420 ($M^+ - OH$, 18.26, ^{37}Cl), 100 ($M^+ - C_6F_{12}Cl$, 100) (Found: C, 27.6; H, 1.05; N, 3.3; F, 52.3. Calc. for $C_{10}H_6ClF_{12}NO_2$: C, 27.55; H, 1.38; N, 3.21; F, 52.35%).

5-(6-*Chloroperfluorohexyl*)-3-*ethyl*-5-*hydroxy*-4,5-*dihydroisozazole* **5h**. δ_F −10 (s, 2 F, CF_2Cl), 43 (m, 8 F, 4 × CF_2) and 44 (AB, J 180, 2 F, CF_2); δ_H 4.6 (m, 1 H, OH), 3.3 (AB, J 22.5, 2 H, cyc-CH_2), 2.8 (q, J 10, 2 H, CH_2), 1.2 (t, J 10, 3 H, CH_3); ν_{max}/cm^{-1} 3200s (OH), 1700m, (C=N), 1200 and 1140s, (C–F); m/z 114 ($M^+ - C_6F_{12}Cl$, 26.91%) and 85 (100) (Found: C, 29.5; H, 1.75; N, 2.9; F, 50.0. Calc. for $C_{11}H_8ClF_{12}NO_2$: C, 29.37; H, 1.79; N, 3.11; F, 50.72%).

Acknowledgements

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