Synthesis of 3-alkyl-5-polyfluoroalkyl-2-isoxazolines via 1,3-dipolar cycloaddition of trimethylsilyl nitronates to polyfluoroalkylethenes

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Abstract

Various 3-alkyl-5-polyfluoroalkyl-2-isoxazoline derivatives have been synthesized in moderate yield by the 1,3-dipolar cycloaddition reaction of nitroalkanes via their trimethylsilyl esters with polyfluoroalkylethenes.

Keywords: Synthesis; Alkylpolyfluoroalkylisoxazolines; 1,3-Dipolar cycloaddition; Trimethylsilyl nitronates; Polyfluoroalkylethenes

1. Introduction

Recently, there has been a growing interest in the synthesis of fluorine-containing heterocyclic compounds because of their potential biological activities [1–3]. Cycloaddition of 1,3-dipoles to carbon–carbon multiple bonds is one of the general methods of preparation of 2-isoxazoline derivatives [4]. Nitrile oxides have been reported to add to perfluoroalkyl-substituted carbon–carbon multiple bonds allowing the synthesis of fluorine-containing heterocyclic compounds [5]. Trimethylsilyl esters of nitroalkanes (nitronates) are a type of 1,3-dipole [6–8] commonly used to prepare 2-isoxazolines which are versatile synthetic intermediates [9–11]. Herein, we report the synthesis of various 3-alkyl-5-polyfluoroalkyl-2-isoxazolines via the 1,3-dipolar cycloaddition of nitronates or trimethylsilyl nitronates to polyfluoroalkylethenes.

2. Results and discussion

Trimethylsilyl nitronates **2a** or **2b** were readily prepared from nitroethane (**1a**) or 1-nitropropane (**1b**), respectively, with chlorotrimethylsilane in benzene. A mixture of a nitronate **2** and a polyfluoroalkylethene **3** with a small amount of triethylamine as stabilizer [7] was stirred at 40–50 °C for about 2 d. A cycloaddition reaction took place and the intermediate 2-trimethyl-

siloxy-3-alkyl-5-polyfluoroalkyl-2-isoxazolidine (**4**) was obtained. On treatment of compound **4** with a catalytic amount of *p*-toluenesulfonic acid at 40 °C for about 2 h, trimethylsilanol elimination occurred and the 2-isoxazoline **5** was obtained in nearly quantitative yield (Method A).

2a-b   **3a-c**

p-TsOH
-Me₃SiOH

4   **5**
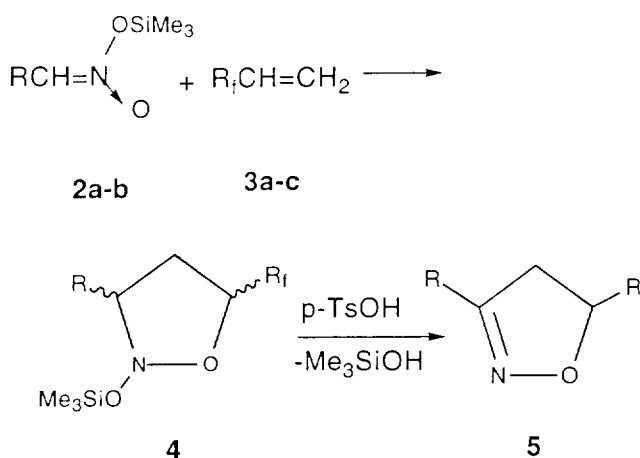
2a, R = CH₃; **2b,** R = C₂H₅; **3a,** R$_f$ = ClC₂F₄;

3b, R$_f$ = ClC₄F₈; **3c,** R$_f$ = ClC₆F₁₂;
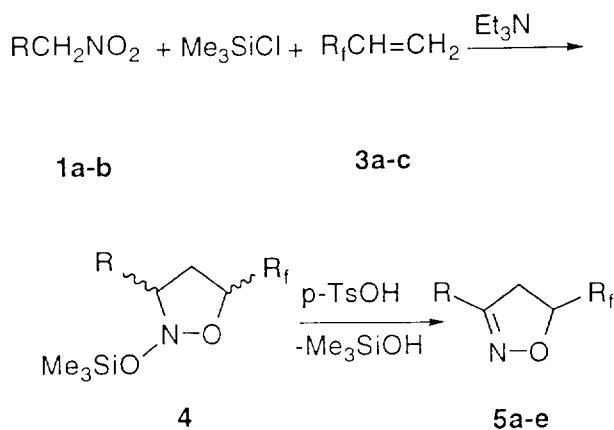
4e, R = C₂H₅, R$_f$ = ClC₆F₁₂.

One example of compound **4** (**4e:** R = C₂H₅, R$_f$ = ClC₆F₁₂) was purified by distillation under reduced

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pressure showing little decomposition. The purified compound **4e** decomposed gradually even on standing. GC showed that compound **4e** was an isomeric mixture; however, after trimethylsilanol elimination, only one definite product **5e** was obtained. This implies that the reaction was regiospecific. The ^{1}H NMR spectrum showed that product **5e** was 3-ethyl-5-(6'-chlorododecafluorohexyl)-2-isoxazoline, since the R_f group was at the C-5 position of the 2-isoxazoline ring and no C-4 R_f-substituted isomer could be detected.

Subsequently, it was found that this three-step sequence, i.e. silylation, dipolar cycloaddition and trimethylsilanol elimination, leading to 2-isoxazoline could be simplified. Thus, the trimethylsilylation of nitroalkanes and the 1,3-dipolar cycloaddition of such nitronates to polyfluoroalkylethenes could be carried out in a one-pot reaction. During trimethylsilylation of nitroalkane **1** with chlorotrimethylsilane in benzene, polyfluoroalkylethene **3** was added to trap the intermediate (the trimethylsilyl ester of the nitroalkane) in situ and the 2-isoxazoline **4** was formed. After acid-catalyzed trimethylsilanol elimination, the 2-isoxazoline **5** was obtained (Method B). Generally speaking, method B gave lower yields than method A. The results are summarized in Table 1.

$$RCH_2NO_2 + Me_3SiCl + R_fCH=CH_2 \xrightarrow{Et_3N}$$

1a-b   **3a-c**

1a, R = CH$_3$; **1b**, R = C$_2$H$_5$;
3a, R$_f$ = ClC$_2$F$_4$; **3b**, R$_f$ = ClC$_4$F$_8$;
3c, R$_f$ = ClC$_6$F$_{12}$.

As shown in Table 1, the cycloaddition reaction proceeded satisfactorily with monosubstituted double bonds. The yields of **5** were not affected by the nature and length of the R_f chain. However, disubstituted carbon–carbon double bonds such as in Br-CF$_2$CF$_2$CH=CHC$_4$H$_9$ and CF$_3$CH=CHOEt either did not react with these 1,3-dipoles or gave rather low yields using Method A or Method B.

Attempted cycloaddition reaction of 2-nitropropane with polyfluoroalkylethene **3c** failed because 2-nitro-

Table 1
Synthesis of 3-alkyl-5-polyfluoroalkyl-2-isoxazolines

Nitroalkanes or ester	$R_fCH=CH_2$	Method	Product	Yields (%)[a]
1a	3a	B	5a	45
1b	3b	B	5b	48
1b	3b	B	5c	50
2b	3b	A	5c	70
1a	3c	B	5d	57
2a	3c	A	5d	72
1b	3c	B	5e	64
2b	3c	A	5e	82

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

propane could not be trimethylsilylated by these methods [7]. In the case of nitromethane, although trimethylation could be achieved by these methods they gave complicated mixtures of cycloaddition products which could not be identified.

It was found that the isoxazolines thus formed have the same structure as those obtained via the 1,3-dipolar cycloaddition of nitrile oxides to perfluoroalkyl alkenes [5]. The CH$_2$ group on the isoxazolinic ring gives an AB spectrum with chemical shifts appearing at 3.2–3.6 ppm, $J_{AB}=18–23$ Hz. The ^{19}F NMR of CF$_2$ adjacent to the asymmetric carbon C-5 often shows an AB pattern ($J_{AB}=300$ Hz) of an ABX spectrum.

In summary, by using the three-step sequence silylation, dipolar addition and trimethylsilanol elimination, or simplified as a one-pot reaction, 2-isoxazoline derivatives may be obtained in moderate yield. The reaction is regiospecific and the 2-isoxazoline formed can be utilized as a useful intermediate to synthesize various kinds of fluorine-containing compounds with multiple functionalities.

3. Experimental details

Infrared spectra were obtained neat on a Shimadzu IR-440 spectrometer using film or KBr plate. ^{19}F NMR spectra were recorded on Varian-360L (56.4 MHz) spectrometer in CDCl$_3$ or acetone-d_6 using CF$_3$CO$_2$H (TFA) as external standard. Chemical shifts in ppm were positive upfield. ^{1}H NMR spectra were obtained on an XL-200 (200 MHz) or a Bruker AC-300 (300 MHz) spectrometer in CDCl$_3$ or acetone-d_6, MS spectra were measured on a Finnigan GC-MS-4021 or Finnigan-8430 spectrometer.

Trimethylsilyl nitronates **2** were prepared from 1-nitroalkanes (**1**) [7]. Trimethylsilyl ester of acid-nitroethane **2a**: b.p. 65–67 °C/25 mmHg. Trimethylsilyl ester of acid-1-nitropropane **2b**: b.p. 60 °C/15 mmHg.

3.1. 1,3-Dipolar cycloaddition reactions of trimethylsilyl nitronates 2 to polyfluoroalkylethenes 3 (Method A): general procedure:

A mixture consisting of 10 mmol of polyfluoroalkylethene **3**, 20 mmol of trimethylsilyl nitronate **2** and 0.5 ml of triethylamine in 20 ml of benzene was stirred at 30–40 °C for about 2 d. The reaction was monitored by ^{19}F NMR spectroscopy. After reaction was complete, the resulting mixture was poured into water (30 ml) and extracted with ethyl acetate (3×20 ml). The combined extract was successively washed with dil. HCl (ca. 1 N, 15 ml), water (20 ml) and brine, and dried over Na_2SO_4. After removal of the solvent, an oily residue (**4**) was obtained. Compound **4e** was distilled to give the pure form. Other residues **4** were directly dissolved in benzene (20 ml) containing 0.5 g of p-toluenesulfonic acid, and the mixture stirred at 40 °C for 2 h. This reaction was monitored by GC (OV-1,3 m). After the reaction was complete, the mixture was poured into water (20 ml) and extracted with ethyl acetate (2×20 ml). The combined extract was washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was distilled to give the pure products **5**.

3.2. 1,3-Dipolar cycloaddition reaction of nitroalkanes 1 with polyfluoroalkylethenes 3 by a one-pot reaction (Method B): general procedure

A mixture consisting of 10 mmol of polyfluoroalkylethene **3**, 20 mmol of nitroalkane **1**, 20 mmol of triethylamine and 20 mmol of chlorotrimethylsilane in 50 ml of benzene was stirred at 30–40 °C for about 2 d. The work-up procedure was the same as for Method A.

2-Trimethylsiloxy-3-ethyl-5-(6'-chlorododecafluoro-hexyl)-2-isoxazolidine (**4e**): b.p. 125–134 °C/2 mmHg. ^{19}F NMR δ: -10 (s, 2F, CF_2Cl); 43 (m, 8F, $4 \times CF_2$); 52 (AB, $J = 300$ Hz, 2F, CF_2) ppm. ^{1}H NMR δ: 5.1–4.7 (m, 1H, 5-H); 3.8–2.7 (m, 3H, 4-H+3-H); 1.6 (m, 2H, CH_2); 1.0 (t, $^3J_{HH} = 7$ Hz, 3H, CH_3); 0.2 (s, 9H, $SiMe_3$) ppm. MS m/z (%): 434 ($M^+ - OSiMe_3$, 2.85); 70 (100). Satisfactory elemental analytical data were difficult to obtain because of decomposition.

3-Methyl-5-(2'-chlorotetrafluoroethyl)-2-isoxazoline (**5a**): b.p. 105–107 °C/12 mmHg. ^{19}F NMR δ: -7 (s, 2F, CF_2Cl); 35 (s, 2F, CF_2) ppm. ^{1}H NMR δ: 5.0 (m, 1H, CH); 3.25 (d, $^3J_{HH} = 8$ Hz, 2H, cyc-CH_2); 2.0 (s, 3H, CH_3) ppm. IR ν_{max} (cm^{-1}): 1720 (m, C=N); 1590 (s, C=N); 1190, 1140 (s, C–F), 720 (s). MS m/z (%): 219 ($M^+ + 1$, 83.72); 69 (CF_3^+, 100). Analysis: $C_6H_6ClF_4NO$ (219.5) requires: C, 32.80; H, 2.73; N, 6.38; F, 34.62%. Found: C, 32.73; H, 2.90; N, 6.20; F, 34.50%.

3-Methyl-5-(4'-chlorooctafluorobutyl)-2-isoxazoline (**5b**): b.p. 112–115 °C/10 mmHg. ^{19}F NMR δ: -8.5 (s, 2F, CF_2Cl); 44 (m, 4F, $2 \times CF_2$); 48 (AB, $J = 300$ Hz, 2F, CF_2) ppm. ^{1}H NMR δ: 5.05 (m, 1H, CH); 3.25 (d, $^3J_{HH} = 8$ Hz, 2H, cyc-CH_2); 2.0 (s, 3H, CH_3) ppm. IR ν_{max} (cm^{-1}): 1720 (m, C=N); 1590 (s, C=N); 1190, 1140 (s, C–F); 720 (s). MS m/z (%): 319 (M^+, 5.37, ^{35}Cl); 321 (M^+, 2.01, ^{37}Cl); 284 ($M^+ - Cl$; 10.93); 84 ($M^+ - C_4F_8Cl$, 51.27); 69 (CF_3^+, 10.57); 56 (100). Analysis: $C_8H_6ClF_8NO$ (319.5) requires: HRMS: 284.0341. Found: 284.0320.

3-Ethyl-5-(4'-chlorooctafluorobutyl)-2-isoxazoline (**5c**): b.p. 112–115 °C/5 mmHg. ^{19}F NMR δ: -8.5 (s, 2F, CF_2Cl); 44 (s, 4F, $2 \times CF_2$); 48 (AB, $J = 300$ Hz, 2F, CF_2) ppm. ^{1}H NMR δ: 5.05 (m, 1H, CH); 3.25 (d, $^3J_{HH} = 8$ Hz, 2H, cyc-CH_2); 2.4 (q, $^3J_{HH} = 4$ Hz, 2H, CH_2); 1.2 (t, $^3J_{HH} = 4$ Hz, 3H, CH_3) ppm. IR ν_{max} (cm^{-1}): 1720 (m, C=N); 1120, 1080 (s, C–F). MS m/z (%): 334 ($M^+ + 1$, 36.54, ^{35}Cl); 336 ($M^+ + 1$, 10.78, ^{37}Cl); 98 ($M^+ - C_4F_8Cl$, 34.81); 70 (100). Analysis: $C_9H_8ClF_8NO$ (333.5) requires: C, 32.38; H, 2.40; N, 4.20; F, 45.58%. Found: C, 32.14; H, 2.42; N, 4.23; F, 45.64%.

3-Methyl-5-(6'-chlorododecafluorohexyl)-2-isoxazoline (**5d**): b.p. 112–115 °C/5 mmHg. ^{19}F NMR δ: -10 (s, 2F, CF_2Cl); 43 (s, 8F, $4 \times CF_2$); 52 (AB, $J = 300$ Hz, 2F, CF_2) ppm. ^{1}H NMR δ: 5.0 (m, 1H, CH); 3.25 (d, $^3J_{HH} = 8$ Hz, 2H, cyc-CH_2); 2.0 (s, 3H, CH_3) ppm. IR ν_{max} (cm^{-1}): 1720 (m, C=N); 1120, 1080 (s, C–F). MS m/z (%): 419 (M^+, 18.48); 84 (100), 69 (CF_3^+, 12.08). Analysis: $C_{10}H_6ClF_{12}NO$ (419.5) requires: HRMS: 418.9936 (^{35}Cl). Found: 418.9945.

3-Ethyl-5-(6'-chlorododecafluorohexyl)-2-isoxazoline (**5e**): b.p. 103–105 °C/2 mmHg. ^{19}F NMR δ: -10 (s, 2F, CF_2Cl); 43 (m, 8F, $4 \times CF_2$); 52 (AB, $J = 300$ Hz, 2F, CF_2) ppm. ^{1}H NMR δ: 5.05 (m, 1H, CH); 3.25 (d, $^3J_{HH} = 8$ Hz, 2H, cyc-CH_2); 2.4 (q, $^3J_{HH} = 4$ Hz, 2H, CH_2); 1.2 (t, $^3J_{HH} = 4$ Hz, 3H, CH_3) ppm. IR ν_{max} (cm^{-1}): 1720 (m, C=N); 1120, 1080 (s, C–F). MS m/z (%): 433 (M^+, 72.47, ^{35}Cl); 435 (M^+, 22.44, ^{37}Cl); 98 ($M^+ - C_6F_{12}Cl$, 6.58); 70 (100). Analysis: $C_{11}H_8ClF_{12}NO$ (433.5) requires: C, 30.45; H, 1.85; N, 3.23; F, 52.60%. Found: C, 30.53; H, 1.68; N, 3.23; F, 52.56%.

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