

# Cycloaddition reactions of *N*-(cyanomethyl)pyridinium ylides with 2,2-dihydropolyfluoroalkanoates

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## Abstract

In the presence of base, 2,2-dihydropolyfluoroalkanoates of type  $R_FCF_2CH_2CO_2Et$  (**2**) react with *N*-(cyanomethyl)pyridinium and *N*-(cyanomethyl)-isoquinolinium ylides (**1**) to give the corresponding indolizine derivatives carrying both a fluoroalkyl and a cyano group (**3**). © 1998 Elsevier Science S.A. All rights reserved.

**Keywords:** Indolizine derivatives; 2,2-Dihydropolyfluoroalkanoates; Cycloaddition

## 1. Introduction

1,3-Dipolar cycloaddition is one of the most important methods of constructing five-membered heterocycles. A number of papers are available on inter- or intra-molecular cycloadditions involving 1,3-dipoles such as nitriloxides, nitrilimines, azides, nitrones, and azomethine ylides with various dipolarophiles [1,2]. However, to the best of our knowledge, and perhaps surprisingly, fluorinated alkenes or alkynes have not been widely studied as dipolarophiles [3–11]. We have recently reported cycloaddition reactions of 2,2-dihydropolyfluoroalkanoates in the presence of a base [12–15]. Owing to the increasing importance of fluorine-containing heterocycles in the field of biology and pharmacology, we have continued that work and also studied the reactions of *N*-(cyanomethyl)pyridinium ylides with 2,2-dihydropolyfluoroalkanoates under basic conditions. Herein, we report our results.

## 2. Results and discussion

The operation is easy and simple. In the presence of triethylamine and potassium carbonate, pyridinium salt and 2,2-dihydropolyfluoroalkanoate in DMF are allowed to react at 65°C for about 8 h to complete the conversion. After conventional work-up and column chromatography,

the indolizine derivatives can be obtained in yields ranging from 20 to 90%, depending on the polyfluoroalkyl group (see Table 1).

Some corresponding reactions involving isoquinolinium *N*-ylides and 2,2-dihydropolyfluoroalkanoates have also been studied (Scheme 1), and the expected indolizines isolated in yields of 48–64% (Table 1). The reactions are believed to proceed via initial formation of the dipolarophile  $R_FCF=CHCO_2Et$  [15].

When  $R_F=ClCF_2$ , the sole products obtained were 2-difluoromethylated indolizines (**3ad–3dd**) instead of the expected 2-chlorodifluoromethyl compounds (see Scheme 2); the process of hydrodechlorination is believed to be analogous to that proposed earlier to account for the formation of difluoromethylated indolizines from  $ClCF_2CF_2CH_2CO_2Et$  and *N*-aminopyridinium iodide under basic conditions [14] (see Scheme 3).

The use of a 3-substituted pyridinium *N*-ylide in this reaction clearly provides the possibility of obtaining either 4- or 6-substituted indolizines. NMR spectra data indicate that 3-methylpyridinium *N*-ylide generated from **1e** produces predominately the 4-methylindolizine **3ea** (see Scheme 4). This regioselectivity is different from that found with the photocycloaddition reactions reported by Sasaki et al. [16] and Tamura et al. [17].

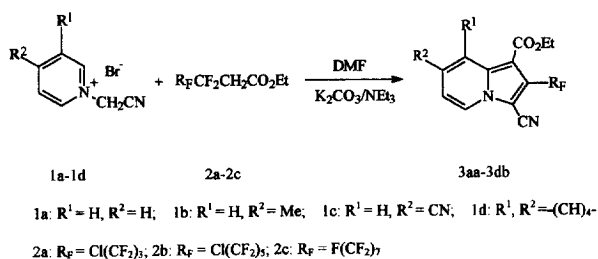
## 3. Experimental

All reagents were of chemical pure or analytical reagent. IR spectra were recorded on an Bio-Rad FTS-20E or FTS

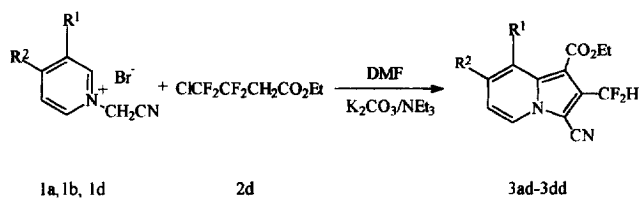
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Table 1  
Yields (isolated material) of compounds of type 3

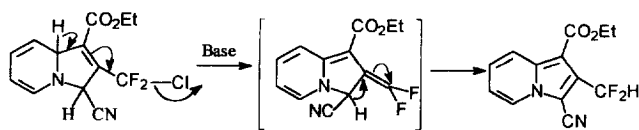
| 1  | R <sup>1</sup>       | R <sup>2</sup> | 2  | R <sub>F</sub>                    | 3: Yield/%        |
|----|----------------------|----------------|----|-----------------------------------|-------------------|
| 1a | H                    | H              | 2a | Cl(CF <sub>2</sub> ) <sub>3</sub> | 3aa: 70           |
| 1a | H                    | H              | 2b | Cl(CF <sub>2</sub> ) <sub>5</sub> | 3ab: 61           |
| 1a | H                    | H              | 2c | F(CF <sub>2</sub> ) <sub>7</sub>  | 3ac: 52           |
| 1a | H                    | H              | 2d | ClCF <sub>2</sub>                 | 3ad: 76           |
| 1b | H                    | Me             | 2a | Cl(CF <sub>2</sub> ) <sub>3</sub> | 3ba: 83           |
| 1b | H                    | Me             | 2b | Cl(CF <sub>2</sub> ) <sub>5</sub> | 3bb: 88           |
| 1b | H                    | Me             | 2d | ClCF <sub>2</sub>                 | 3bd: 90           |
| 1c | H                    | CN             | 2b | Cl(CF <sub>2</sub> ) <sub>5</sub> | 3cb: 20           |
| 1d | -(CH) <sub>4</sub> - |                | 2a | Cl(CF <sub>2</sub> ) <sub>3</sub> | 3da: 63           |
| 1d | -(CH) <sub>4</sub> - |                | 2b | Cl(CF <sub>2</sub> ) <sub>5</sub> | 3db: 64           |
| 1d | -(CH) <sub>4</sub> - |                | 2d | ClCF <sub>2</sub>                 | 3dd: 48           |
| 1e | Me                   | H              | 2a | Cl(CF <sub>2</sub> ) <sub>3</sub> | 3ea: 68; 3ea': 13 |



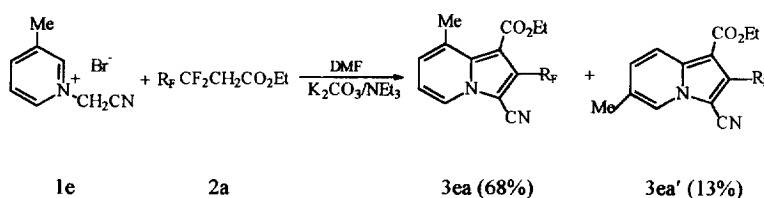
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

185 spectrophotometer, using KBr pellets. <sup>1</sup>H NMR spectra were measured on Bruker AM 300 (300 MHz) spectrometer, using TMS as internal standard. <sup>19</sup>F NMR spectra were recorded on a Varian EM-360L spectrometer (56.4 MHz) using TFA as external standard, positive chemical shift values (in ppm) being assigned to absorptions upfield and the values reported as δ<sub>CFCl<sub>3</sub></sub> (δ<sub>CFCl<sub>3</sub></sub> = δ<sub>TFA</sub> + 76.8). Mass spectra were recorded on a Finnegan GC-MS 4021 spectrometer. Column chromatography was performed using silica gel H, particle size 10–40 μm.

### 3.1. Typical procedure

A mixture of 1.1 mmol of *N*-(cyanomethyl)pyridinium salt (**1a**) [18,19], 1 mmol of ethyl 2,2-dihydropolyfluoroalkanoate (**2a**), 1.5 mmol of triethylamine and 1.5 mmol of potassium carbonate in 5 ml of DMF were stirred at 60°C for about 8 h to complete the conversion. After it had been cooled to room temperature, the reaction mixture was acidified with 1 M aqueous HCl (to pH 6). The solution was extracted with dichloromethane (3×30 cm<sup>3</sup>), the organic phases were combined and washed with saturated brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue obtained was purified by column chromatography using light petroleum ether (bp: 60–90°C) and ethyl acetate (4:1) as eluant to give **3aa**.

### 3.2. 3aa

ν<sub>max</sub>: 3121, 2994, 2227 (C≡N), 1695 (C=O), 1121–1276 (C–F) cm<sup>-1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>): 8.44 (d, <sup>3</sup>J<sub>HH</sub> = 9 Hz, 1H, C5–H), 8.42 (d, <sup>3</sup>J<sub>HH</sub> = 7 Hz, 1H, C8–H), 7.44–7.17 (m, 2H, Ar–H), 4.40 (q, 2H, –OCH<sub>2</sub>–), 1.36 (t, 3H, –CH<sub>3</sub>) ppm; δ<sub>F</sub> (CDCl<sub>3</sub>): 66.3 (m, 2F), 100.3 (m, 2F), 117.3 (s, 2F) ppm; *m/z*: 398 (M<sup>+</sup>, 100.0), 370 (34.7), 353 (64.7), 326 (24.8); C<sub>15</sub>H<sub>9</sub>ClF<sub>6</sub>N<sub>2</sub>O<sub>2</sub> Calcd: C, 45.2; H, 2.3; N, 7.0; F, 28.6 Found: C, 45.9; H, 2.6; N, 6.8; F, 28.0%.

### 3.3. 3ab

ν<sub>max</sub>: 2227 (C≡N), 1696 (C=O), 1089–1241 (C–F) cm<sup>-1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>): 8.48 (d, <sup>3</sup>J<sub>HH</sub> = 9 Hz, 1H, C5–H), 8.42 (d, <sup>3</sup>J<sub>HH</sub> = 7 Hz, 1H, C8–H), 7.43–7.15 (m, 2H, Ar–H), 4.39 (q, 2H, –OCH<sub>2</sub>–), 1.36 (t, 3H, –CH<sub>3</sub>) ppm; δ<sub>F</sub> (CDCl<sub>3</sub>): 66.8 (m, 2F), 100.8 (m, 2F), 117.8–121.3 (m, 6F) ppm; *m/z*: 498

(M<sup>+</sup>, 48.9), 470 (27.9), 453 (82.8), 426 (34.5), 215 (100.0), 190 (40.3); C<sub>17</sub>H<sub>9</sub>ClF<sub>10</sub>N<sub>2</sub>O<sub>2</sub> Calcd: C, 41.0; H, 1.8; N, 5.6; F, 38.2 Found: C, 41.0; H, 1.8; N, 5.4; F, 38.5%.

### 3.4. 3ac

$\nu_{\max}$ : 3119, 2993, 2227 (C≡N), 1698 (C=O), 1104–1277 (C–F) cm<sup>-1</sup>;  $\delta$ H (CDCl<sub>3</sub>): 8.49 (d, <sup>3</sup>J<sub>HH</sub>=9 Hz, 1H, C5–H), 8.42 (d, <sup>3</sup>J<sub>HH</sub>=7 Hz, 1H, C8–H), 7.44–7.18 (m, 2H, Ar–H), 4.41 (q, 2H, –OCH<sub>2</sub>–), 1.39 (t, 3H, –CH<sub>3</sub>) ppm;  $\delta$ F (CDCl<sub>3</sub>): 80.3 (s, 3F), 100.8 (m, 2F), 118.3–125.8 (m, 10F) ppm; *m/z*: 582 (M<sup>+</sup>, 94.1), 554 (39.1), 537 (100.0), 510 (46.8), 215 (86.3); C<sub>19</sub>H<sub>9</sub>F<sub>15</sub>N<sub>2</sub>O<sub>2</sub> Calcd: C, 39.2; H, 1.6; N, 4.8; F, 49.0 Found: C, 39.2; H, 1.5; N, 4.6; F, 48.8%.

### 3.5. 3ad

$\nu_{\max}$ : 3102, 2982, 2218 (C≡N), 1701 (C=O), 1115–1268 (C–F) cm<sup>-1</sup>;  $\delta$ H (CDCl<sub>3</sub>): 8.38 (m, 2H, C5–H+C8–H), 7.41–7.14 (m, 3H, Ar–H+CF<sub>2</sub>H), 4.41 (q, 2H, –OCH<sub>2</sub>–), 1.44 (t, 3H, –CH<sub>3</sub>) ppm;  $\delta$ F (CDCl<sub>3</sub>): 110.8 (d, *J*=60 Hz, 2F) ppm; *m/z*: 264 (M<sup>+</sup>, 89.9), 236 (50.7), 219 (100.0), 192 (39.3); C<sub>13</sub>H<sub>10</sub>ClF<sub>2</sub>N<sub>2</sub>O<sub>2</sub> Requires: 264.0710 HRMS Found: 264.0708.

### 3.6. 3ba

$\nu_{\max}$ : 2995, 2227 (C≡N), 1696 (C=O), 1108–1277 (C–F) cm<sup>-1</sup>;  $\delta$ H (CDCl<sub>3</sub>): 8.25 (d, <sup>3</sup>J<sub>HH</sub>=8 Hz, 1H, C5–H), 8.20 (s, 1H, C8–H), 7.00 (d, <sup>3</sup>J<sub>HH</sub>=8 Hz, 1H, C6–H), 4.35 (q, 2H, –OCH<sub>2</sub>–), 2.55 (s, 3H, –Ar–CH<sub>3</sub>), 1.40 (t, 3H, –CH<sub>3</sub>) ppm;  $\delta$ F (CDCl<sub>3</sub>): 65.8 (t, 2F), 99.8 (t, 2F), 116.8 (s, 2F) ppm; *m/z*: 412 (M<sup>+</sup>, 100.0), 367 (36.1), 229 (56.3); C<sub>16</sub>H<sub>11</sub>ClF<sub>6</sub>N<sub>2</sub>O<sub>2</sub> Calcd: C, 46.6; H, 2.7; N, 6.8; F, 27.6 Found: C, 46.6; H, 2.6; N, 6.8; F, 27.6%.

### 3.7. 3bb

$\nu_{\max}$ : 2989, 2224 (C≡N), 1693 (C=O), 1103–1299 (C–F) cm<sup>-1</sup>;  $\delta$ H (CDCl<sub>3</sub>): 8.35 (d, <sup>3</sup>J<sub>HH</sub>=8 Hz, 1H, C5–H), 7.30 (s, 1H, C8–H), 7.05 (d, <sup>3</sup>J<sub>HH</sub>=8 Hz, 1H, C6–H), 4.40 (q, 2H, –OCH<sub>2</sub>–), 2.55 (s, 3H, Ar–CH<sub>3</sub>), 1.55 (t, 3H, –CH<sub>3</sub>) ppm;  $\delta$ F (CDCl<sub>3</sub>): 67.3 (t, 2F), 100.8 (s, 2F), 119.3 (m, 6F) ppm; *m/z*: 512 (M<sup>+</sup>, 100.0), 467 (73.6), 440 (40.2), 229 (45.9); C<sub>18</sub>H<sub>11</sub>ClF<sub>10</sub>N<sub>2</sub>O<sub>2</sub> Calcd: C, 42.2; H, 2.2; N, 5.5; F, 37.1 Found: C, 42.7; H, 2.1; N, 5.6; F, 37.0%.

### 3.8. 3bd

$\nu_{\max}$ : 3060, 2982, 2216 (C≡N), 1717 (C=O), 1697, 1114–1298 (C–F) cm<sup>-1</sup>;  $\delta$ H (CDCl<sub>3</sub>): 8.25 (d, <sup>3</sup>J<sub>HH</sub>=7 Hz, 1H, C5–H), 8.13 (s, 1H, C8–H), 7.61–7.25 (t, *J*=60 Hz, 1H, CF<sub>2</sub>H), 6.95 (d, <sup>3</sup>J<sub>HH</sub>=7 Hz, 1H, C6–H), 4.39 (q, 2H, –OCH<sub>2</sub>–), 2.50 (s, 3H, –Ar–CH<sub>3</sub>), 1.43 (t, 3H, –CH<sub>3</sub>) ppm;  $\delta$ F (CDCl<sub>3</sub>): 110.8 (d, *J*=60 Hz, 2F) ppm; *m/z*: 278 (M<sup>+</sup>, 100.0), 251 (14.0), 233 (56.1); C<sub>14</sub>H<sub>12</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub> Calcd:

C, 60.4; H, 4.4; N, 10.1; F, 13.7 Found: C, 60.3; H, 4.2; N, 10.0; F, 14.2%.

### 3.9. 3cb

$\nu_{\max}$ : 3103, 2998, 2236 (C≡N), 1692 (C=O), 1135–1299 (C–F) cm<sup>-1</sup>;  $\delta$ H (CDCl<sub>3</sub>): 8.85 (s, 1H, C8–H), 8.45 (d, <sup>3</sup>J<sub>HH</sub>=8 Hz, 1H, C5–H), 7.25 (d, <sup>3</sup>J<sub>HH</sub>=8 Hz, 1H, C6–H), 4.45 (q, 2H, –OCH<sub>2</sub>–), 1.45 (t, 3H, –CH<sub>3</sub>) ppm;  $\delta$ F (CDCl<sub>3</sub>): 67.3 (t, 2F), 101.3 (t, 2F), 42.5 (m, 6F) ppm; *m/z*: 523 (M<sup>+</sup>, 83.6), 495 (41.6), 478 (89.6), 451 (27.9), 272 (42.5), 240 (100.0), 215 (43.8); C<sub>18</sub>H<sub>8</sub>ClF<sub>10</sub>N<sub>3</sub>O<sub>2</sub> Requires: 523.0145 HRMS Found: 523.0166.

### 3.10. 3da

$\nu_{\max}$ : 2995, 2933, 2221 (C≡N), 1729 (C=O), 1120–1289 (C–F) cm<sup>-1</sup>;  $\delta$ H (CDCl<sub>3</sub>): 8.07 (m, 1H, C10–H), 8.04 (d, <sup>3</sup>J<sub>HH</sub>=8 Hz, 1H, C5–H), 7.64–7.17 (m, 4H, Ar–H), 4.35 (q, 2H, –OCH<sub>2</sub>–), 1.23 (t, 3H, –CH<sub>3</sub>) ppm;  $\delta$ F (CDCl<sub>3</sub>): 66.8 (m, 2F), 102.8 (m, 2F), 118.8 (m, 2F) ppm; *m/z*: 448 (M<sup>+</sup>, 100.0), 431 (60.3), 403 (99.0), 265 (75.5), 215 (87.0, 1); C<sub>19</sub>H<sub>11</sub>ClF<sub>6</sub>N<sub>2</sub>O<sub>2</sub> Requires: 448.0413 HRMS Found: 448.0404.

### 3.11. 3db

$\nu_{\max}$ : 2220 (C≡N), 1737 (C=O), 1106–1205 (C–F) cm<sup>-1</sup>;  $\delta$ H (CDCl<sub>3</sub>): 8.22 (m, 1H, C10–H), 8.09 (d, <sup>3</sup>J<sub>HH</sub>=8 Hz, 1H, C5–H), 7.77–7.29 (m, 4H, Ar–H), 4.39 (m, 2H, –OCH<sub>2</sub>–), 1.42 (t, 3H, –CH<sub>3</sub>) ppm;  $\delta$ F (CDCl<sub>3</sub>): 66.8 (m, 2F), 103.3 (m, 2F), 119.3 (m, 6F) ppm; *m/z*: 548 (M<sup>+</sup>, 100.0), 503 (85.7), 476 (39.9), 265 (70.1), 121 (75.8); C<sub>21</sub>H<sub>11</sub>ClF<sub>10</sub>N<sub>2</sub>O<sub>2</sub> Calcd: C, 46.0; H, 2.0; N, 5.1; F, 34.6 Found: C, 46.1; H, 1.8; N, 5.2; F, 34.8%.

### 3.12. 3dd

$\nu_{\max}$ : 3133, 2987, 2225 (C≡N), 1721 (C=O), 1100–1272 (C–F) cm<sup>-1</sup>;  $\delta$ H (CDCl<sub>3</sub>): 8.65 (m, 1H, C10–H), 7.86 (d, <sup>3</sup>J<sub>HH</sub>=7 Hz, 1H, C5–H), 7.50–7.13 (m, 5H, CF<sub>2</sub>H+Ar–H), 3.98 (q, 2H, –OCH<sub>2</sub>–), 0.96 (t, 3H, –CH<sub>3</sub>) ppm;  $\delta$ F (CDCl<sub>3</sub>): 110.3 (d, *J*=60 Hz, 2F) ppm; *m/z*: 314 (M<sup>+</sup>, 72.9), 286 (22.5), 269 (100.0), 242 (48.9); C<sub>17</sub>H<sub>12</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub> Requires: 314.0866 HRMS Found: 314.0903.

### 3.13. 3ea'

$\nu_{\max}$ : 2220 (C≡N), 1728 (C=O), 1124–1291 (C–F) cm<sup>-1</sup>;  $\delta$ H (CDCl<sub>3</sub>): 8.35 (d, <sup>3</sup>J<sub>HH</sub>=9 Hz, 1H, C8–H), 8.21 (s, 1H, C5–H), 7.27 (d, <sup>3</sup>J<sub>HH</sub>=9 Hz, 1H, C7–H), 4.39 (q, 2H, –OCH<sub>2</sub>–), 2.44 (s, 3H, Ar–CH<sub>3</sub>), 1.36 (t, 3H, –CH<sub>3</sub>) ppm;  $\delta$ F (CDCl<sub>3</sub>): 66.3 (t, 2F), 99.8 (t, 2F), 116.8 (s, 2F) ppm; *m/z*: 412 (M<sup>+</sup>, 100.0), 384 (37.4), 367 (80.7), 340 (47.2), 229 (74.3); C<sub>16</sub>H<sub>11</sub>ClF<sub>6</sub>N<sub>2</sub>O<sub>2</sub> Requires: 412.0413 HRMS Found: 412.0447.

### 3.14. 3ea

$\nu_{\max}$ : 3095, 2995, 2219 (C≡N), 1732 (C=O), 1116–1286 (C–F)  $\text{cm}^{-1}$ ;  $\delta\text{H}$  ( $\text{CDCl}_3$ ): 8.24 (d,  $^3J_{\text{HH}}=7$  Hz, 1H, C5–H), 7.01 (m, 2H, Ar–H), 4.40 (q, 2H,  $-\text{OCH}_2-$ ), 2.48 (s, 3H, Ar–CH<sub>3</sub>), 1.35 (t, 3H,  $-\text{CH}_3$ ) ppm;  $\delta\text{F}$  ( $\text{CDCl}_3$ ): 65.3 (t, 2F), 102.8 (t, 2F), 117.8 (s, 2F) ppm;  $m/z$ : 412 ( $\text{M}^+$ , 96.8), 384 (30.8), 367 (100.0), 340 (46.4), 229 (48.3);  $\text{C}_{16}\text{H}_{11}\text{ClF}_6\text{N}_2\text{O}_2$  Calcd: C, 46.6; H, 2.7; N, 6.8; F, 27.6 Found: C, 46.5; H, 2.8; N, 6.7; F, 27.5%.

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