Introduction of a difluoromethylene group into organic compounds has been observed to impart them with positive properties, as viewed by a wide range of industries. Here, synthesis of 3,3-difluoro-2-pyrrolidone derivatives (7) was accomplished by the reaction of ethyl 2,2-difluoro-4-iodo-4-(trimethylsilyl) butanolate (4) with primary amines followed by desilylation. The key intermediate (4) was prepared from the addition reaction of trimethylvinylsilane (3) to ethyl difluoriodoacetate (2) in the presence of Cu(0). Ethyl difluoriodoacetate (2) was prepared starting from ethyl bromodifluoroacetate (1) via Reformatsky-type reaction.

Key Words: 3,3-Difluoro-2-pyrrolidone, α,α-Difluoro-γ-lactam, Difluoromethylene group

Results and Discussion

Eguchi et al., synthesized 3,3-difluoro-2-pyrrolidone from methyl 4-azido-2,2-difluorobutanate via ring formation by PPh₃ or PBu₃. When the reaction was proceeded in toluene with PPh₃, an intermediate, 4,4-difluoro-3,4-dihydro-5-methoxy-2H pyrrole, was formed first. But, it was prone to...
be hydrolyzed to yield 3,3-difluoro-2-pyrrolidone. Use of more nucleophilic PbBu₃ in dried THF gave only 3,3-difluoro-1-methyl-2-pyrrolidone without an intermediate. Based on this finding, it is expected that further variation of the –OR group in alkyl 4-azido-2,2-difluorobutanoate could yield N-substituted 3,3-difluoro-2-pyrrolidone. However, use of azid derivatization and intrinsic low yields are significant drawbacks in practice applications.

In our retrosynthetic analysis of 3,3-difluoro-2-pyrrolidone, ethyl iododifluoroacetate, trimethyl(vinyl)silane and primary amines were chosen as potential starting materials. (Figure 1). Reaction of ethyl bromodifluoroacetate, Zn, I₂ and HgCl₂ in triglyme solution gave ethyl iododifluoroacetate in 64% yield, but we encountered a further problem removing the solvent. Under acetonitrile solvent, however, the same reaction required only Zn, I₂ at 0 °C to give ethyl iododifluoroacetate in 90% yield.

Addition reaction of ethyl iododifluoroacetate (2) to vinyl trimethylsilane (3) under the Cu(0) catalyst resulted in the formation of ethyl 2,2-difluoro-4-iodo-4-(trimethylsilyl)butanoate (4) in 91% yield. The reaction involves a radical mechanism in which a single electron transfer occurs, as reported by Yang et al. Then, (4) reacted with various primary amines (5) to yield N-alkyl-3,3-difluoro-5-trimethylsilyl-2-pyrrolidones (6) (Scheme 1). These results are summarized in Table 1. As can be seen, the smaller alkyl primary amines the better the yields. This is a result of a steric effect between the bulky trimethylsilyl group and the alkyl group of amine. Removal of the trimethylsilyl group occurred by the addition KF. The reaction of (6) with KF at 100 °C resulted in N-alkyl-3,3-difluoro-2-pyrrolidones in good yields (Table 1).

All the products were identified using ¹H NMR, ¹³C NMR, ¹⁹F NMR and MS spectra. ¹⁹F NMR spectra of all the adducts showed typical AB splitting patterns, because the two fluorines are not equivalent because of the presence of the γ-positioned chiral center. For instance, ²JFF coupling constant of (6) observed in ¹⁹F-NMR showed a typically high value of 262 Hz, which would reflect diasterotopic fluorine atoms on the ring system. When trimethyl groups were removed, therefore, the coupling constants between fluorine atoms in (7) appeared as nullified, giving a singlet ¹⁹F-NMR signal. This would imply that fluorine atoms in 3,3-difluoro-2-pyrrolidone (7) become enantiotopic atoms as

**Table 1. Preparation of N-alkyl-3,3-difluoro-5-trimethylsilyl-1-2-pyrrolidones (6) and N-alkyl-3,3-difluoro-2-pyrrolidones (7)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reactant (R-NH₂)</th>
<th>Yield of (6)</th>
<th>Yield of (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>H</td>
<td>6a 72</td>
<td>7b 74</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>n-C₄H₉</td>
<td>6b 70</td>
<td>7b 74</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Cyclohexyl</td>
<td>6c 81</td>
<td>7c 75</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>CH₃CH₂H₅</td>
<td>6d 67</td>
<td>7d 70</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>CH₃CH₂CH₂H₅</td>
<td>6e 75</td>
<td>7e 80</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>CH₃CH₂H₅(m-F)(p-F)</td>
<td>6f 71</td>
<td>7f 79</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>CH₃CH₂H₅(o-F)</td>
<td>6g 72</td>
<td>7g 75</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>CH₃CH₂H₅(p-F)</td>
<td>6h 77</td>
<td>7h 82</td>
</tr>
</tbody>
</table>

**Figure 1. Retrosynthesis of 1-Alkyl-α,α-difluoro-2-pyrrolidone.**

**Scheme 1**

<table>
<thead>
<tr>
<th>R</th>
<th>(a)</th>
<th>(b)</th>
<th>(c)</th>
<th>(d)</th>
<th>(e)</th>
<th>(f)</th>
<th>(g)</th>
<th>(h)</th>
</tr>
</thead>
</table>
the chiral center (trimethylsilyl) group was removed.

Conclusions

Ethyl 2,2-difluoro-4-iodo-4-(trimethylsilyl)butanolate (4) was reacted with primary amines (5) to yield a series of N-alkyl-3,3-difluoro-5-trimethylsilyl-2-pyrrolidones (6), which was reacted further with KF at 100 °C to result in the formation of N-alkyl-3,3-difluoro-2-pyrrolidones (7) via the removal of the trimethylsilyl group. Our synthetic platform appears suitable for preparing noble fluorinated lactam derivatives to explore their highly branched and fluorinated analogues for pharmaceutical applications.

Experimental

General. 19F NMR were recorded on a Jeol JNM-ECP 500 MHz or Bruker AC-300 (282.44 MHz). Spectra were recorded on the AC-300 spectrometer. All samples were taken in CDCl3 solvent and all chemical shifts are reported in parts per million downfield (positive) of the standard: TMS of 1H and 13C; CFCl3 for 19F NMR. FT-IR spectra were recorded as CCl4 solutions and reported in wavenumber (cm⁻¹). GC-MS spectra were obtained at 70 eV in the electron impact mode (Shimadzu GC 17A-QP5000). Infrared spectra were obtained with a Jasco FT-IR-5300 Spectrophotometer.

Preparation of Cu(0) catalyst. To a 500 mL Erlenmeyer flask [S2] was introduced 200 mL of carbon tetrachloride, 40 g of copper powder and 15 g of iodine. The solution was stirred until it was colorless and filtered with a Buchner funnel. The Cu(0) catalyst obtained was washed with a solution of acetone and concentrated hydrochloric acid (500 mL, 1:1) followed by rinsing with acetone 3 to 5 times. It was then dried before being stored in a dried bottle under nitrogen.

Ethyl 2,2-difluoro-4-iodo-4-(trimethylsilyl)butanolate (4). 12.5 g of ethyl iododifluoro-acetate (50.00 mmol), 10.00 g of trimethylvinylsilane (100.00 mmol) and 2.5 g of activated copper powder (2.5 mmol) were added to 200 mL of acetonitrile dried over phosphorus pentoxide. The reaction mixture was stirred 15 hrs at 65 °C. The reaction mixture was purified by flash column chromatography (silica gel 60F-254, ethyl acetate:n-hexane = 1:3). HRMS: C11H21NOF2Si, Calculated, 249.13605; Observed, 249.13442.

1H NMR (CDCl3) δ 0.11 (s, 9H), 2.25 (J = 8.3, 15.5, 15.5, 22.5 Hz, 1H), 2.59 (J = 6.9, 6.9, 14.2, 18.3 Hz, 1H), 3.12 (dd, J = 7.4, 7.4, 1.8 Hz, 1H), 7.79 (s). 13C NMR (CDCl3) δ = -5.0, 19.0, -39.5, 69.9, 129.0, 133.9, 142.0, 145.6, 161.7, 167.3 (t, 30.7 Hz). 19F NMR (CDCl3) δ = -4.4, 32.9 (t, 22.4 Hz), 39.1, 118.3 (t, 259.4 Hz), 167.3 (t, 30.7 Hz). 13F NMR (CDCl3) δ = -108.4 (dd, J = 266.5, 15.0, 6.4 Hz), -106.9 (dd, J = 266.5, 19.3, 19.3 Hz). FT-IR (CCl4): 1256 (s), 1427 (m), 2961 (s) cm⁻¹. GC-MS m/z (relative intensity): 55.05 (19.90), 73.00 (100), 115.00 (38.34), 191.95 (M+ + 1, 0.38). HRMS: C7H13NOF2Si, Calculated, 193.07345; Observed, 193.07237.

1-Butil-3,3-difluoro-5-iodomethyl-2-pyrrolidone (6b). 1H NMR (CDCl3) δ 0.14 (s, 9H), 0.92 (t, 5.4 Hz, 3H), 1.30 (m, 2H), 1.53 (m, 2H) 2.56 (dd, J = 8.0, 10.5, 14.6, 17.0 Hz, 1H), 2.24 (dd, J = 7.1, 14.5, 16.5, 17.9 Hz, 1H), 2.87 (dd, J = 2.0, 4.9, 6.8, 8.8 Hz, 1H), 3.20 (dd, J = 2.3, 7.7 Hz, 1H), 3.90 (dd, J = 7.9, 13.6, 16.4 Hz, 1H). 13C NMR (CDCl3) δ = 3.0, 13.9, 20.0, 28.9, 32.0 (t, 23.0), 42.8, 43.3, 118 (t, 249.5), 164.19 (t, 30.7). 19F NMR (CDCl3) δ = -106.2 (dd, J = 266.0, 10.3, 17.6 Hz), -105.4 (dd, J = 266.0, 17.6, 17.6 Hz). FT-IR (CCl4): 1259 (s), 1427 (m), 1722, 2966 (s) cm⁻¹. GC-MS m/z (relative intensity): 57 (27.33) 73.00 (100), 86 (13.99), 120 (0.30), 128 (2.86), 250 (M+ + 1, 0.09). HRMS: C7H11NOF2Si, Calculated, 249.13605; Observed, 249.13442.

1-Cyclohexyl-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6c). 1H NMR (CDCl3) δ 0.15 (s, 9H), 1.11-1.24 (m, 3H), 2.04-1.60 (m, 6H), 2.34-2.23 (m, 2H), 2.55 (m, 1H), 3.06 (m, 1H), 3.15 (m, 1H). 13C NMR (CDCl3) δ = -2.61 (3c), 24.97, 25.90, 26.0, 28.38, 28.94, 32.34 (t, 23.0 Hz), 44.85, 58.15, 118.24 (t, 249.5 Hz), 163.4 (t, 30.7 Hz). 19F NMR (CDCl3) δ = -104.98 (dd, J = 263.5, 12.6, 18.0 Hz), -102.88 (dd, J = 263.5, 12.6, 18.0 Hz). FT-IR (CCl4): 1286 (s), 1429 (m), 1718 (m), 2962 (s), 3156 (s) cm⁻¹. GC-MS m/z (relative intensity): 55.05 (72.13) 73.00 (100), 100.95 (81.96), 192.05 (25.17), 275.0 (1.98, M+), 276.05 (1.24). HRMS: C11H21NOF2Si, Calculated, 275.15170; Observed, 275.15091.

1-Benzyl-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6d). 1H NMR (CDCl3) δ 0.11 (s, 9H), 2.31 (dd, J = 30.7, 15.7, 6.4 Hz, 1H), 2.53 (dd, J = 30.7, 15.7, 8.7 Hz, 1H), 3.09 (dd, J = 8.7, 6.4 Hz, 1H), 3.92 (d, 15.4 Hz, 1H), 5.30 (d, 15.4 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.33 (m, 4H). 13C NMR (CDCl3) δ = -2.9 (s), 32.0 (t, 23.0 Hz), 42.6, 47.0, 118.3 (t, 249.5 Hz), 127.7, 128.2, 129.1, 134.8, 164.6 (t, 30.7 Hz). 19F NMR (CDCl3) δ = -105.39 (dd, J = 265.0, 15.7, 15.7 Hz), -104.82 (dd, J = 265.0, 15.7, 15.7 Hz). FT-IR (CCl4): 1258 (s), 1431 (m), 1722 (m), 2957 (s) cm⁻¹. GC-MS m/z (relative intensity): 73.05 (100) 91.00 (88.40), 192.05 (34.54), 282.95 (M+ + 1, 0.13). HRMS: C14H19NOF2Si, 283.95 (M+ + 1, 0.13).
N-(2-Phenylethyl)-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6e). 1H NMR (CDCl₃, TMS): δ 0.16 (s, 9H), 2.47-2.75 (m, 2H), 2.00 (dd, J = 11.9 Hz, 2.3 Hz, 1H), 2.58-2.76 (m, 2H), 0.14 (s, 9H). 13C NMR (CDCl₃, TMS): δ 163.86 (t, J = 3.8 Hz), 150.19 (dd, J = 12.4 Hz, 3.8 Hz), 150.19 (dd, J = 248.0 Hz, 12.4 Hz), 133.74 (t, J = 3.8 Hz), 128.38 (s), 130.61 (d, J = 16.4 Hz, 3.8 Hz), 117.88 (s), 117.84 (t, J = 253.7 Hz), 117.81 (t, J = 17.2 Hz), 117.15 (d, J = 18.1 Hz), 42.83 (s), 37.78 (t, J = 23.8 Hz), 29.79 (s).

N-(3,4-Difluorobenzyl)-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6f). 1H NMR (CDCl₃, TMS): δ 1.71-1.75 (m, 3H), 4.46 (m, 2H), 3.00 (dd, J = 11.9 Hz, 2.3 Hz, 1H), 2.58-2.76 (m, 2H), 0.14 (s, 9H). 13C NMR (CDCl₃, TMS): δ 163.86 (t, J = 28.6 Hz, 150.55 (dd, J = 248.0 Hz, 12.4 Hz), 150.19 (dd, J = 248.0 Hz, 12.4 Hz), 133.74 (t, J = 3.8 Hz), 128.38 (s), 130.61 (d, J = 3.8 Hz), 117.88 (s), 117.84 (t, J = 253.7 Hz), 117.81 (t, J = 17.2 Hz), 117.15 (d, J = 18.1 Hz), 42.83 (s), 37.78 (t, J = 23.8 Hz), 29.79 (s).

N-(2-Fluorobenzyl)-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6g). 1H NMR (CDCl₃, TMS): δ 0.11 (s, 9H), 2.42-2.51 (m, 2H), 3.36 (t, J = 6.5 Hz, 1H), 4.58 (s, 2H), 7.04-7.16 (m, 4H). 13C NMR (CDCl₃, TMS): δ 2.21 (s, 9H), 2.80 (s), 37.86 (s), 21.9 Hz). 1H NMR (CDCl₃, TMS): δ 0.11 (1H, m), 1.69 (1H, m), 1.39 (2H, m), 1.75 (2H, m). 13C NMR (CDCl₃, TMS): δ 165.86 (t, J = 3.8 Hz), 150.24 (dd, J = 12.4 Hz, 3.8 Hz), 150.24 (dd, J = 248.0 Hz, 12.4 Hz), 133.74 (t, J = 3.8 Hz), 128.38 (s), 130.61 (d, J = 3.8 Hz), 162.22 (t, J = 253.7 Hz), 163.77 (t, J = 28.6 Hz). 13F NMR (CDCl₃, CFCF₃): δ −104.12 (dd, J = 252.4, 23.3 Hz, 1F), −105.58 (dd, J = 252.4, 23.3, 1F). IR (KBr): 2955, 1687, 1562, 1493, 1251, 1197, 1105 cm⁻¹. GC-MS (m/z, relative intensity): HRMS: C₁₄H₁₇NOF₄Si, Calculated, 319.10156; Observed, 319.10147.

N-(2-Phenethyl)-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (7d). 1H NMR (CDCl₃, TMS): δ 7.19-7.32 (m, 5H), 3.60 (t, J = 7.3 Hz, 2H), 3.18 (t, J = 6.4 Hz, 2H), 2.91 (t, J = 7.3 Hz, 2H), 2.35-2.41 (m, 2H). 13C NMR (CDCl₃, TMS): δ 163.60, (t, J = 37.4 Hz), 137.96 (s), 128.85 (s), 128.69 (s), 126.95 (s), 117.92 (t, J = 243.5 Hz), 45.35 (s), 20.41 (s), 29.38 (s), 29.38 (s), 29.19 (t, J = 22.9 Hz). 19F NMR (CDCl₃, CFCF₃): δ −105.46 IR (KBr): 2991, 1736, 1678, 1614, 1537, 1233, 1273 cm⁻¹. GC-MS (m/z, relative intensity): 255 (M⁺), 134 (11.65), 104 (90.6), 91 (21.67), 77 (18.12), 42 (100.0).

N-(3,4-Difluorobenzyl)-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (7e). 1H NMR (CDCl₃, TMS): δ 6.7-6.7 Hz, 4.77, 13.3 (15.1), 3.3, 2H), 3.22 (s, 2H), 7.25 (m, 3H), 13.1 (11.65), 129.69 (s), 128.69 (s), 126.95 (s), 117.92 (t, J = 243.5 Hz), 45.35 (s), 20.41 (s), 29.38 (s), 29.38 (s), 29.19 (t, J = 22.9 Hz). 19F NMR (CDCl₃, CFCF₃): δ −105.46 IR (KBr): 2991, 1736, 1678, 1614, 1537, 1233, 1273 cm⁻¹. GC-MS (m/z, relative intensity): 225 (M⁺), 350, 134 (11.65), 104 (90.6), 91 (21.67), 77 (18.12), 42 (100.0).

N-(4-Fluorobenzyl)-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (7f). 1H NMR (CDCl₃, TMS): δ 6.7-6.7 Hz, 4.77, 13.3 (15.1), 3.3, 2H), 3.22 (s, 2H), 7.25 (m, 3H), 13.1 (11.65), 129.69 (s), 128.69 (s), 126.95 (s), 117.92 (t, J = 243.5 Hz), 45.35 (s), 20.41 (s), 29.38 (s), 29.38 (s), 29.19 (t, J = 22.9 Hz). 19F NMR (CDCl₃, CFCF₃): δ −105.46 IR (KBr): 2991, 1736, 1678, 1614, 1537, 1233, 1273 cm⁻¹. GC-MS (m/z, relative intensity): 225 (M⁺), 350, 134 (11.65), 104 (90.6), 91 (21.67), 77 (18.12), 42 (100.0).
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References and Notes


