Synthesis of 3,3-Difluoro-2-pyrrolidone Derivatives

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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 difluoroiodoacetate (**2**) in the presence of Cu(0). Ethyl difluoroiodoacetate (**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

Introduction

Organic compounds containing a difluoromethylene group often display significant physiological properties, such as antibiotic,[2] and an inhibitory effect on various enzymes,[1] the human immunodeficiency virus, or HIV,[3] cancers and hypertension.[4] These desirable properties stem from difluoromethylene's strong carbon-fluorine bond and its lipophilicity.

In general, we incorporated a difluoromethylene group into organic compounds, using the following reactions: (a) the addition of perfluoroalkyl iodide to alkenes, performed in the presence of various catalysts, such as titanium,[5] benzoylperoxide,[6] sodium dithionite[7] and organophosphines[8] (b) the Reformatsky reaction, which was used to prepare α,α-difluoro-β-hydroxy carbonyl compounds from the reaction of aldehydes with α-chloro-α,α-difluoromethyl ketones[9] or α-bromo-α,α-difluoro acetates[10] (c) the addition of ethyl bromodifluoroacetate to alkenes, carried out using nickel chloride or copper powder as a catalyst.[11] (d) the transformation of carbonyl group to difluoromethylene group, utilizing (diethylamino)sulfur trifluoride, or DAST.[12] Researchers recently reported that difluoromethylene ketone could be introduced into the electron-deficient olefins, using UV irradiation[13] and that palladium catalyst has been used for difluoromethylene ketone addition to electron-rich olefins.[14]

Derivatives of pyrrolidones comprising peripheral difluoromethylene are also regarded as key building blocks for biologically important compounds. Naturally occurring pyrrolidones have been found to be anti-microbial, anti-tumor, and anti-histamine.[15]

Brahms and Dailey reported that although difluoromethylene resembles methylene in appearance, compounds possessing difluoromethylene show different properties from those possessing methylene.[16] And they observed that while it is well known that fluorine is the most electronegative element, the idea that fluorine can donate electron density to a π system, using one of its lone pairs, is not as well appreciated. For instance, fluorine can act as a slightly activating *ortho-para* director in electrophilic aromatic substitution, and the substitution reaction on nitrogen in 3,3-difluoro-2-pyrrolidone, which is in a *meta*-position, would not be preferred in mild reaction conditions.[16] Recently, Eguchi *et al.* performed cyclization of difluoro-GABA *via* Staudinger/intramolecular-aza-Wittig approach of its azido-ester with trialkylphosphine.[15] The reaction of azoester with PPh_3 in toluene at room temperature gave α,α-difluoro-butanlactam in *ca.* 36% yield. There are, in addition, only a few examples of difluoromethylene bearing γ-lactams reported.[17,18]

It is noted that a direct substitution reaction on the 3,3-difluoro-2-pyrrolidone should be avoided in developing a high-yield synthetic route. Therefore, we adapted a cyclization method that could incorporate various substituents of biological importance to the nitrogen atom of pyrrolidone during ring formation. That is, ethyl 2,2-difluoro-4-iodo-4-(trimethylsilyl)butanolate (**4**) and primary amines are allowed to react for the preparation of *N*-substituted difluoropyrrolidones[19] (Figure 1). In the present report, we detail the synthesis of a series of noble *N*-alkyl 3,3-difluoro-2-pyrrolidon derivatives.

Results and Discussion

Eguchi *et al.* synthesized 3,3-difluoro-2-pyrrolidone from methyl 4-azido-2,2-difluorobutanoate *via* ring formation by PPh_3 or PBu_3.[17] When the reaction was proceeded in toluene with PPh_3, an intermediate, 4,4-difluoro-3,4-dihydro-5-methoxy-2*H* pyrrole, was formed first. But, it was prone to

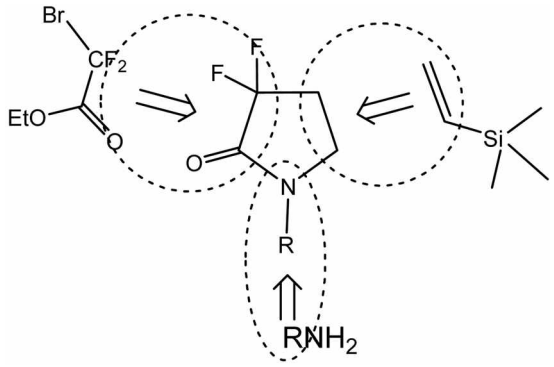


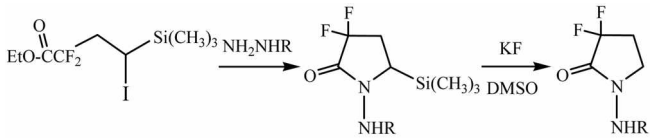
Figure 1. Retrosynthesis of 1-Alkyl-α,α-difluoro-2-pyrrolidone.

be hydrolyzed to yield 3,3-difluoro-2-pyrrolidone. Use of more nucleophilic PBu_3 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, I_2 and $HgCl_2$ in triglyme solution gave ethyl iododifluoroacetate in 64% yield,[20] but we encountered a further problem removing the solvent. Under acetonitrile solvent, however, the same reaction required only Zn, I_2 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)-butanolate (**4**) in 91% yield. The reaction involves a radical mechanism in which a single electron transfer occurs, as reported by Yang *et al.*[17] 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

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

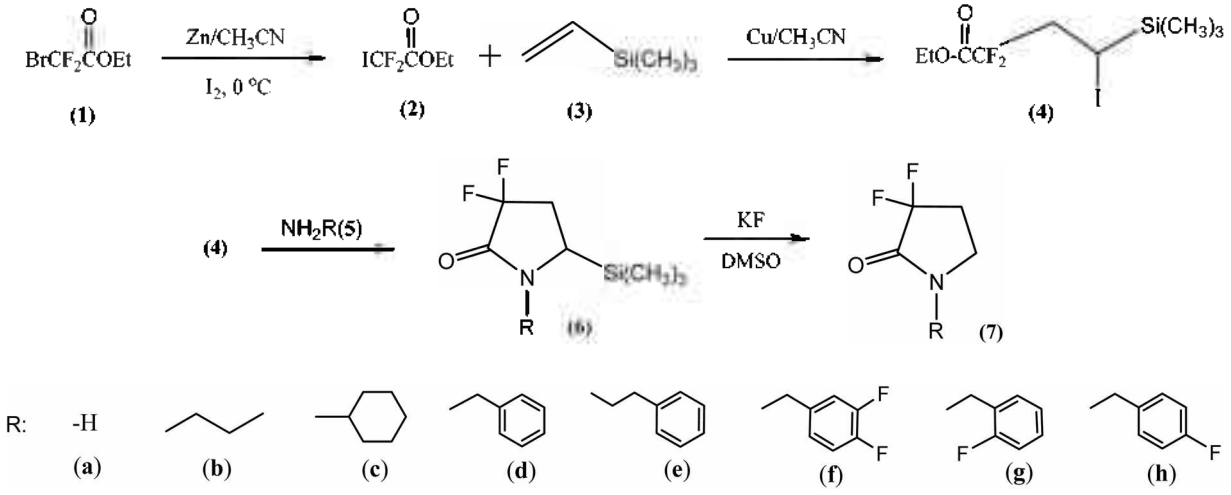


(4) (6) (7)

Entry	Substrate	Reactants(R-NH_2)	(6)	Yield of (6)*	(7)	Yield of (7)*
1	**4**	H	6a	72	–	–
2	**4**	*n*-C_4H_9	6b	70	7b	74
3	**4**	Cyclohexyl	6c	81	7c	75
4	**4**	$CH_2C_6H_5$	6d	67	7d	70
5	**4**	$CH_2CH_2C_6H_5$	6e	75	7e	80
6	**4**	$CH_2C_6H_4$(*m*-F)(*p*-F)	6f	71	7f	79
7	**4**	$CH_2C_6H_5$(*o*-F)	6g	72	7g	75
8	**4**	$CH_2C_6H_5$(*p*-F)	6h	77	7h	82

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 ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and MS spectra. ^{19}F 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, $^2J_{FF}$ coupling constant of (**6**) observed in ^{19}F-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 ^{19}F-NMR signal. This would imply that fluorine atoms in 3,3-difluoro-2-pyrrolidone (**7**) become enantiotopic atoms as



Scheme 1

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. ^{19}F 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 $CDCl_3$ solvent and all chemical shifts are reported in parts per million downfield (positive) of the standard: TMS of ^{1}H and ^{13}C; $CFCl_3$ for ^{19}F NMR. FT-IR spectra were recorded as CCl_4 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)butanoate (4). 12.5 g of ethyl iododifluoro-aceate (50.00 mmol), 10.00 g of trimethylvinylsilane (100.0 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, R_f= 0.68) to afford ethyl 2,2-difluoro-4-iodo-4-(trimethylsilyl)butanoate (15.6 g, 91%) as a colorless liquid.

^{1}H NMR ($CDCl_3$) δ: 0.18 (s, 9H), 1.38 (t, 7.1 Hz, 3H), 2.60 (m, 2H), 3.11 (t, 6.6Hz, 1H), 4.36 (q, 7.1Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: −2.42, 4.41 (t, 4.2 Hz), 13.94, 39.16 (t, 24.2 Hz), 63.19, 115.74 (t, 252.6 Hz), 163.77 (t, 31.9 Hz). ^{19}F NMR ($CDCl_3$) δ: −108.6 (dt, J = 73.0 Hz, 17.1 Hz), −102.3 (ddd, J = 261 Hz, 14.6 Hz, 12.2 Hz). FT-IR (CCl_4): 1095 (s), 1191 (s), 1254 (s), 1761 (s), 1744 (s), 2960 (m) cm^{-1} GC-MS m/z (relative intensity): 73 (78.0), 77 (53.7), 84 (25.7), 103 (100), 185 (5.5), 350 (M^+ 2.3). HRMS: C9H21O2F2ISi, Calculated, 354.03237; Observed, 354.03193.

3,3-Difluoro-5-trimethylsilyl-2-pyrrolidone (6a). 1.00 g of ethyl 2,2-difluoro-4-iodo-4-(trimethylsilyl)butanoate (2.80 mmol) was added to 4.50 mL of aqueous ammonium hydroxide solution (28%, 4.70 mmol) and stirred for 24 hrs. The reaction products were extracted with diethyl ether and separated by TLC (alumina 60F, ethyl acetate:n-hexane = 1:3, R_f = 0.67). 0.42 g of **6a** was isolated as a colorless liquid. (Yield: 72%) To prepare **6b** to **6h**, the same procedure was applied varying only the amines, and the yields of products are noted in Table 1.

^{1}H NMR ($CDCl_3$) δ: 0.11 (s, 9H), 2.25 (J = 8.3, 15.5, 15.5, 22.5 Hz, 1 Hz), 2.59 (J = 6.9, 6.9, 14.2, 18.3 Hz, 1 Hz), 3.12 (ddd, J = 7.4, 7.4, 1.8 Hz, 1 Hz), 7.79 (s). ^{13}C NMR ($CDCl_3$) δ: −4.4, 32.9 (t, 22.4 Hz), 39.1, 118.3 (t, 259.4 Hz), 167.3 (t, 30.7 Hz). ^{19}F NMR ($CDCl_3$) δ: −108.4 (ddd, J = 266.5, 15.0, 6.4 Hz), −106.9 (ddd, J = 266.5, 19.3, 19.3 Hz). FT-IR (CCl_4): 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+, 1.94), 192.95 (M^+ +1, 0.38). HRMS: C7H13NOF2Si, Calculated, 193.07345; Observed, 193.07237.

1-Butyl-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6b). ^{1}H NMR ($CDCl_3$) δ: 0.14 (s, 9H), 0.92 (t, 5.4 Hz, 3H), 1.30 (m, 2H), 1.53 (m, 2H) 2.56 (dddd, J = 8.0, 10.5, 14.6, 17.0 Hz, 1H), 2.24 (dddd, J = 7.1 14.5, 16.5, 17.9 Hz, 1H), 2.87 (dddd, J = 2.0, 4.9, 6.8, 8.8 Hz, 1H), 3.20 (ddd, J = 2.3, 7.7 7.7 Hz, 1H), 3.90 (ddd, J = 7.9, 13.6, 16.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) 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). ^{19}F NMR ($CDCl_3$) δ: −106.2 (ddd, J = 266.0, 10.3, 17.6 Hz), −105.4 (ddd, J = 266.0, 17.6, 17.6 Hz). FT-IR (CCl_4): 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^+, 0.09). HRMS: C11H21NOF2Si, Calculated, 249.13605; Observed, 249.13442.

1-Cyclohexyl-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6c). ^{1}H NMR ($CDCl_3$) δ: 0.15 (s, 9H), 1.14-1.24 (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). ^{13}C NMR ($CDCl_3$) 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). ^{19}F NMR ($CDCl_3$) δ: −104.98 (ddd, J = 263.5, 12.6, 18.0 Hz), −102.88 (ddd, J = 263.5, 12.6, 18.0 Hz). FT-IR (CCl_4): 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: C13H23-NOF2Si, Calculated, 275.15170; Observed, 275.15091.

1-Benzyl-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6d). ^{1}H NMR ($CDCl_3$) δ: 0.11(s, 9H), 2.31(ddd, J = 30.7, 15.7, 6.4 Hz, 1H), 2.53 (ddd, 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). ^{13}C NMR ($CDCl_3$) 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). ^{19}F NMR ($CDCl_3$) δ: −105.39 (ddd, J = 265.0, 15.7, 15.7 Hz), −104.82 (ddd, J = 265.0, 15.7, 15.7 Hz). FT-IR (CCl_4): 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^+, 0.79), 283.95 (M^+ + 1, 0.13). HRMS: C14H19NOF2Si,

Calculated, 283.12040; Observed, 283.11998.

***N*-(2-Phenylethyl)-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6e).** ^{1}H NMR ($CDCl_3$, TMS): δ 0.16 (s, 9H), 2.47-2.75 (m, 2H), 2.87 (t, J = 6.9 Hz, 2H), 2.97 (dd, J = 11.5, 2.8 Hz, 1H), 3.59-3.63 (m, 2H), 7.21-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, TMS): δ −2.37 (s), 4.90 (s), 35.29 (s), 37.79 (t, J = 23.8 Hz), 40.75 (s), 117.74 (t, J = 254.4 Hz), 126.90 (s), 128.83 (s), 128.88 (s), 138.09 (s), 163.71 (t, J = 38.4 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −104.05 (dd, J = 253.0, 23.0 Hz, 1F), −105.58 (dd, J = 253.0, 23.0, 1F). FT-IR (CCl_4): 2955, 1693, 1680, 1542, 1442, 1205, 1188, 1082 cm^{-1}. HRMS: C15H21NOF2Si, Calculated, 297.13605; Observed, 297.13584.

***N*-(3,4-Difluorobenzyl)-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6f).** ^{1}H NMR ($CDCl_3$, TMS): δ 7.13-7.15 (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). ^{13}C NMR ($CDCl_3$, TMS): δ 163.86 (t, J = 28.6 Hz), 150.55 (dd, J = 248.0 Hz, J = 12.4 Hz), 150.19 (dd, J = 248.0 Hz, J = 12.4 Hz), 133.74 (t, J = 3.8 Hz), 124.13 (dd, J = 6.6 Hz, J = 3.8 Hz), 118.78 (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), −2.39 (s). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −104.12 (dd, J = 252.4, 23.3 Hz, 1F), −105.66 (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-Fluorobenzyl)-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6g).** ^{1}H NMR ($CDCl_3$, TMS): δ 0.11 (s, 9H), 2.42-2.51 (m, 2H), 3.36 (t, J = 6.5 Hz, 1H), 4.58 (s, 2H), 7.04-7.36 (m, 4H). ^{13}C NMR ($CDCl_3$, TMS): δ −2.39 (s), 29.80 (s), 37.86 (t, J = 23.8 Hz), 43.88 (s), 115.76 (d, J = 21.0 Hz), 117.79 (t, J = 243.2 Hz), 123.76 (d, J = 15.2 Hz), 124.53 (d, 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). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −104.38 (dd, J = 253.0, 34.5 Hz, 1F), −105.58 (dd, J = 253.0, 34.5 Hz, 1F). IR (KBr); 1105, 1197, 1251, 1493, 1562, 1687, 2955 cm^{-1}. GC-MS (m/z, relative intensity): 45 (11.70), 73 (30.91), 83 (12.04), 109 (100.0), 140 (7.69), 210 (4.10), 275 (4.54), 301 (M^+, 3.37). HRMS: C14H17NOF4Si, Calculated, 301.11098; Observed, 301.11137.

***N*-(4-Fluorobenzyl)-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (6h).** ^{1}H NMR ($CDCl_3$, TMS): δ 7.02-7.29 (m, 4H), 4.43-4.53 (m, 2H), 3.01 (dd, J = 11.5 Hz, 2.3 Hz, 1H), 2.54-2.79 (m, 2H), 0.16 (s, 9H). ^{13}C NMR ($CDCl_3$, TMS): δ 163.71 (t, J = 27.7 Hz), 162.56 (t, J = 246.1 Hz), 132.49 (d, J = 2.9 Hz), 129.94 (d, J = 8.6 Hz), 117.81 (t, J = 253.7 Hz), 115.88 (d, J = 21.9 Hz), 43.15 (s), 37.84 (t, J = 23.8 Hz), 29.79 (s), −2.39 (s). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −105.77 (s, 2F), −119.13 (s, 1F). IR (KBr); 2959, 1682, 1606, 1512, 1439, 1251, 1192, 1126 cm^{-1}. GC-MS (m/z, relative intensity): 301 (M+, 3.37), 109 (100.0), 83 (8.49), 73 (13.35), 53 (8.79). HRMS: C14H17NOF4Si, Calculated, 301.11098; Observed, 301.11006.

1-Butyl-3,3-difluoro-2-pyrrolidone (7b). 0.82 g of 1-butyl-3,3-difluoro-5-trimethylsilyl-2-pyrrolidone (3.26 mmol), 15 mL of DMSO and 0.76 g of KF (13.1 mmol) were placed in a 30 mL flask and allowed to react at 100 °C for 24 hrs., or to react along with 6.52 mL/1.0 M THF (6.52 mmol) of Bu_4NF (tetrabutylammonium fluoride) for 12 hrs. The reaction products were extracted by ether, dried over anhydrous $MgSO_4$. Thin layer chromatography (alumina 60F-254, ethyl acetate: *n*-hexane = 1:3, R_f = 0.67) resulted in separation of 0.41 g (2.28 mmol) of **7a** (yield of 70%). To prepare **7c** to **7h**, the same procedure was applied, and the yields of products are noted in Table 2.

^{1}H NMR ($CDCl_3$) δ: 0.19 (t, 7.3 Hz, 9H), 1.61 (dt, 7.3 Hz, 2H), 1.53 (t, 7.3 Hz, 2H), 2.48 (dddd, J = 6.7, 6.7, 15.0, 15.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 13.8, 20.0, 28.9, 29.4 (t, 22.6 Hz), 41.3 (br), 43.5, 118.3 (t, 249.5 Hz), 163.6 (t, 30.7 Hz). ^{19}F NMR ($CDCl_3$) δ: −105.8 (dd, 15.0, 15.0 Hz). FT-IR (CCl_4): 1262 (s), 1427 (s), 1719 (s), 2973 (s) cm^{-1}. GC-MS m/z (rel. intensity): 57 (20.20), 106 (43.83), 120 (14.61), 177 (M+, 37.20). HRMS: C8H13NOF2, Calculated, 177.09652; Observed, 177.09451.

1-Cyclohexyl-3, 3-difluoro-2-pyrrolidone (7c). ^{1}H NMR ($CDCl_3$) δ: 1.11 (1H, m), 1.69 (1H, m), 1.39 (2H, m), 1.75 (2H, m), 1.82 (2H, m), 2.46 (2H, dddd, 6.9, 13.3, 15.2, 15.2 Hz), 3.38 (2H), 3.97 (1H, m). ^{13}C NMR ($CDCl_3$) δ: 25.16 (2c), 25.21 (1c), 29.3 (1c, t, 23.0 Hz), 29.7 (2c), 37.2 (br, 1c), 51.7 (1c), 118.5 (1c, t, 249.5 Hz), 62.9 (1c, 31.4 Hz). ^{19}F NMR ($CDCl_3$) δ: −105.99 (dd, 16.4). FT-IR (CCl_4): 1216 (m), 1431 (m), 1715 (s) cm^{-1}. GC-MS m/z (rel. intensity): 82 (11.58), 120 (0.49), 122 (100), 203 (M^+, 6.12). HRMS: C10H15NOF2, Calculated, 203.11217; Observed, 203.11228.

1-Benzyl-3,3-difluoro-2-pyrrolidone (7d). ^{1}H NMR ($CDCl_3$) δ: 2.47(2H, dddd, 6.7, 6.7, 13.3, 15.1), 3.30 (2H, dd, 6.7, 6.7 Hz), 4.52 (s, 2H), 7.25 (2H, m), 7.35 (3H, m). ^{13}C NMR ($CDCl_3$) δ: 29.3 (t, 23.0 Hz), 40.8, 47.7, 118.3 (t, 250.5 Hz), 128.47 (1c), 128.51 (2c), 129.2 (2c), 134.7, 163.7 (t, 31.7). ^{19}F NMR ($CDCl_3$) δ: −105.7 (dd, 14.3, 14.3). FT-IR (CCl_4): 1435 (s), 1262 (s), 1723 (m), 2979 (s) cm^{-1}. GC-MS m/z relative intensity): 65 (15.70), 91 (100), 120 (0.52), 76 (0.73), 211 (M^+, 34.56).

***N*-(2-Phenyl ethyl)-3,3-difluoro-2-pyrrolidone (7e).** ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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), 42.14 (s), 33.37 (s), 29.39 (t, J = 22.9 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −105.46 IR (KBr); 2991, 1736, 1678, 1614, 1537, 1323, 1273 cm^{-1}. GC-MS (m/z, relative intensity): 225 (M^+, 3.50), 134 (11.65), 104 (90.65), 91 (21.67), 77 (18.12), 42 (100.0).

***N*-(3,4-Difluorobenzyl)-3,3-difluoro-2-pyrrolidone (7f).** ^{1}H NMR ($CDCl_3$, TMS): δ 6.98-7.18 (m, 4H), 4.47 (s, 2H), 3.32 (t, J = 6.4 Hz, 1H), 2.46-2.52 (m, 2H). ^{13}C NMR ($CDCl_3$, TMS): δ 163.63 (t, J = 31.5 Hz), 151.45 (dd, J = 249.0 Hz, J = 13.4 Hz), 149.45 (dd, J = 248.0 Hz, J = 13.4 Hz), 131.71 (t, J = 4.7 Hz), 124.49 (dd, J = 6.7 Hz, J = 3.8 Hz), 118.04 (s), 117.90 (t, J = 254.5 Hz), 117.34 (t, J = 17.2 Hz), 46.66 (s), 40.77 (s), 29.18 (t, J = 24.1 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −105.85 (s, 2F), −136.69 (s, 1F), −138.88 (s, 1F). IR (KBr); 2916, 1724, 1620, 1520, 1435, 1284,

1261, 1116, 1010 cm^{-1}. GC-MS (m/z, relative intensity): 247 (M^+, 24.87), 168 (6.54), 127 (100.0), 101 (11.25), 77 (11.79), 56 (6.71), 42 (12.29).

***N*-(2-Fluorobenzyl)-3,3-difluoro-2-pyrrolidone (7g).** ^1H NMR ($CDCl_3$, TMS): δ 2.41-2.51 (m, 2H), 3.35 (t, J = 6.4 Hz, 1H), 4.58 (s, 2H), 7.05-7.36 (m, 4H). ^{13}C NMR ($CDCl_3$, TMS): δ 29.19 (t, J = 23.8 Hz), 40.97 (s), 47.56 (s), 115.71 (d, J = 21.0 Hz), 118.03 (t, J = 247.9 Hz), 128.36 (d, J = 4.8 Hz), 129.10 (s), 130.37 (d, J = 8.5 Hz), 130.94 (d, J = 2.9 Hz), 161.13 (d, J = 245.1 Hz), 163.57 (t, J = 30.5 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −105.77 (s, 2F), −119.13 (s, 1F). IR (KBr); 1099, 1126, 1255, 1349, 1494, 1728, 2928 cm^{-1}. GC-MS (m/z, relative intensity): 56 (4.78), 77 (3.31), 83 (16.69), 109 (100.0), 150 (3.43), 158 (2.82), 229 (M^+, 20.07).

***N*-(4-Fluorobenzyl)-3,3-difluoro-2-pyrrolidone (7h).** ^1H NMR ($CDCl_3$, TMS): δ 2.44-2.49 (m, 2H), 3.29 (t, J = 6.4 Hz, 2H), 4.49 (s, 2H), 7.01-7.06 (m, 2H), 7.20-7.26 (m, 2H). ^{13}C NMR ($CDCl_3$, TMS): δ 29.17 (t, J = 23.8 Hz), 40.63 (s), 46.88 (s), 116.08 (d, J = 21.9 Hz), 118.06 (t, J = 254.0 Hz), 130.17 (d, J = 8.5 Hz), 130.49 (d, J = 1.0 Hz), 162.71 (t, J = 246.1 Hz), 163.69 (t, J = 32.4 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −105.88 (s, 2F), −114.08 (s, 1F). IR (KBr); 1116, 1226, 1435, 1512, 1606, 1711, 2937 cm^{-1}. GC-MS (m/z, relative intensity): 57 (5.35), 77 (3.84), 83 (16.25), 109 (100.0), 150 (5.82), 158 (6.31), 229 (M, 23.82).

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