ADDITION-ELIMINATION REACTION OF HIGHLY ELECTROPHILIC DIFLUOROOLEFIN, 5-DIFLUOROMETHYLENE-3-PYRROLIN-2-ONES

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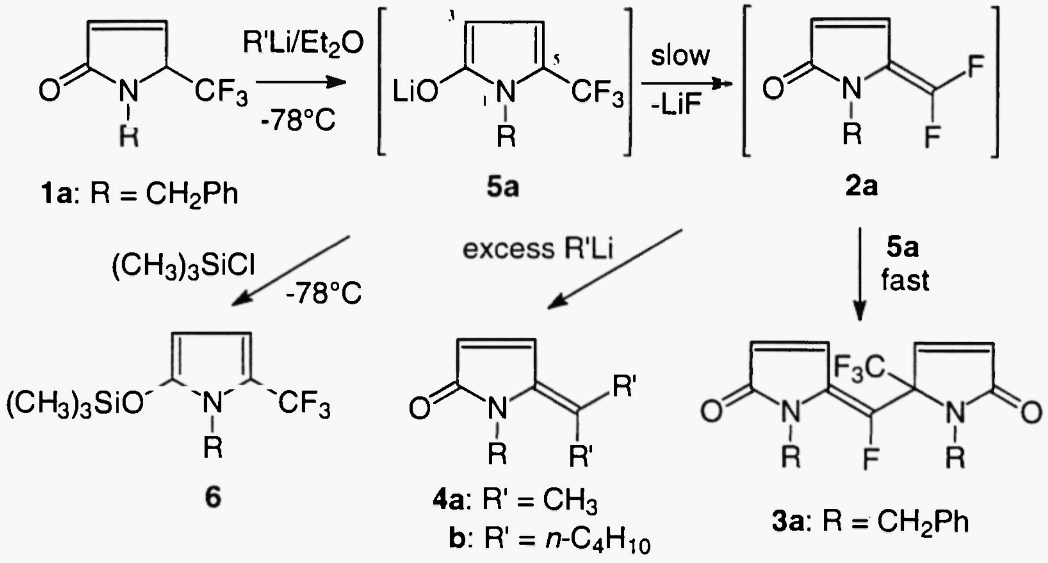
Abstract: 1-Alkyl-5-difluoromethylene-3-pyrroline-2-ones **2** were generated from 1-alklyl-5-trifluoromethyl-3-pyrrolin-2-ones **1** via dehydrofluorination with methyllithium at -78 °C. Spontaneous addition-elimination reaction of **2** with enolate anion of **1** gave fluorinated pyrrolinonylmethylidenepyrrolinones **3**.

Geminally difluorinated olefins are relatively reactive chemical species because of the repulsive interaction between nonbonding lone pairs of fluorine atoms and *p*-orbitals of the CC π-bond (1). In the continuous effort of the synthesis of fluorine-containing heterocycles, we have recently reported the synthesis of trifluoromethylated pyrrolinone **1a** by an acidic dehydration of 1-benzyl-5-hydroxy-5-trifluoromethyl-2-pyrrolidinone, a ring-chain tautomer of 1-benzyl-5,5,5-trifluoro-4-oxopentanoyl amide, and the consecutive migration of the formed double bond to the thermodynamically more stable **1a** (2). The hydrogen of 5-position of pyrrolinone **1** can be readily eliminated because of conjugation with carbonyl group, and E_1cb mechanism would yield an interesting heterocyclic difluoroolefin **2a**. We report here formation of 5-difluoromethylenepyrrolinone **2** and the spontaneous addition-elimination reaction of enolate anion of **1a** (3).

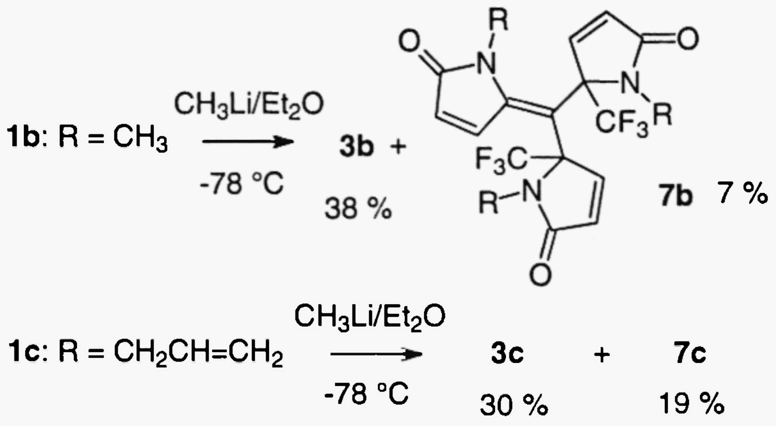
We attempted at first dehydrofluorination of **1a** with an equimolar amount of CH_3Li at -78 °C. Since the reaction mixture turned to a black tar material when it was allowed to warm up to room temperature, water was added in one portion to the mixture at -78 °C to quench the strong base. However, the desired difluoroolefin **2a** was not found in the reaction mixture, and the spectral data revealed that the product was pyrrolinonylmethylidenepyrrolinone **3a** (80 % yield). Mass spectrum showed the product was a dimer of **2a** (*m/z*: 442) though the ^1H and the ^{13}C NMR spectra were relatively complicated. In the ^{19}F NMR spectrum, there is a pair of a doublet (J = 20 Hz, 3F) and a quartet (J = 20 Hz; 1F), and a weak doublet of qualtets signal at $\delta = 72.43$ ($J_{^{13}C\text{-}^{19}F}$ = 30, 26 Hz) was found in the ^{13}C NMR spectrum. These signals indicate that **3a** has a $CF_3\text{–}\underline{C}CF$ substructure being assigned based on the unsymmetrical nature of the NMR spectra (4). Stereochemistry of the



Scheme 1

tetrasubstituted olefin was determined as *Z* according to the long-range H-F coupling (*J* = 3 Hz) of the vinylic fluorine and one of two benzyl groups. This product was also given in the reaction with an excess of DBU at -78 °C in 56 % yield. The regioselectivity of enolate **5a** is somewhat surprising because 5-position of **5a** is the most sterically hindered site. Dimerization of angelicalactones at room temperature occurs at both 3- and 5-positions while the 5-position of angelicalactone is far less crowded than that of **5a**(5). Michael dimerization of trifluoroangelicalactone also occurs only at 5-position (6). Probably, the trifluoromethyl group plays a role of anchor to localize the anionic center of the enolate at adjacent carbon by the strong electron-withdrawing effect, and the α-position reactivity of electron-rich pyrrole was enhanced. Moreover, the product is thermodynamically more stable than the product reacted at 3-position. When threefold amount of CH_3Li was used at -78 °C, a small amount of isopropylidene derivative **4a** was also isolated (5 %) as well as the major product **3a** (24 %). The reaction of **1a** with threefold amount of BuLi gave also the dibutylmethylene derivative **4b** as the major product (19 %) and **3a** (7 %). These results strongly suggest that the difluoromethylenepyrrolinone **2a** was actually generated although **2a** was reactive even at low temperature in the presence of nucleophiles such as alkyl lithium to give alkylidenepyrrolinones **4** or enolate **5a** to give **3a** via the successive addition - elimination mechanism of the difluoroolefin (Scheme 1).

Since no isopropylidenepyrrolinone **4a** was yielded when an equimolar amount of CH_3Li was used for the dehydrofluorination, the Li enolate **5a** was considered to be kinetically stable at -78 °C. Thus, chlorotrimethylsilane was added at -78 °C just after addition of CH_3Li into the reaction mixture, and trimethylsiloxypyrrole **6** was observed in the ^{1}H NMR spectrum [$\delta = 0.15$: $-Si(CH_3)_3$] of



Scheme 2

the pentane-soluble portion of the resulting mixture, in which neither peaks of **2a** nor dimers **3a** were observed, although isolation of **6** failed due to hydrolysis to **1a**. However, after 6 h at -78 °C, hydrogen chloride ethereal solution was added to the solution of **5a**, and the products were protonated **1a** (56 %) and product **3a** (44 %). Since no chlorodifluoromethylpyrrolinone was observed in the reaction mixture analyzed by GC-MS, the elimination of fluoride anion from enolate **5a** occurs at -78 °C slowly, and once **2a** is generated, it immediately reacts with another molecule of **5a** except the presence of an excess of highly reactive nucleophiles such as alkyl lithium.

Dehydrofluorination with CH_3Li followed by spontaneous addition-elimination of **1b** and **1c** with less sterically demanding *N*-alkyl groups (**1b**: R = methyl, **1c**: R = allyl) at -78 °C gave complex mixtures, including dimeric products **3b** (*m*/*z*: 290) and **3c** (*m*/*z*: 342), and trimeric products **7b** (*m*/*z*: 435) and **7c** (*m*/*z*; 513) (Scheme 2)(7). This means the vinyl fluoride structure in **3** is still reactive for the enolate **5** unless the steric effect of substituent on *N*-1 of pyrrolinone is absent.

In conclusion, dehydrofluorination of trifluoromethylated pyrrolinone **1** by alkyl lithium or other bases actually gives the corresponding difluoromethylenepyrrolinone **2** as a reactive intermediate. However, in the presence of nucleophile, further addition-elimination reaction of **1** gave alkylidenepyrrolinones **4**, pyrrolinonylmethylidenepyrrolinones **3**, and bispyrrolinonylmethylidenepyrrolinones **7**.

Experimental detail for the synthesis of 3a:

To a stirred solution of pyrrolinone **2a** (120 mg, 0.5mmol) in Et_2O (10 ml) at -78 °C under N_2 atmosphere, 1.05M CH_3Li ethereal solution (0.48 mL, 0.5 mmol) was slowly added, and the resulting solution was stirred at -78 °C for 1 h. To the stirred solution, water (1 mL) at room temperature was added in one portion. After warming up to room temperature, the mixture was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on a SiO_2 column eluting with hexane - EtOAc (2 : 1) to give a colorless solid (92 mg, 80%): M.p. 106 - 107 °C; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS) $\delta = 4.43$ (d, $J = 16$ Hz, 1 H), 4.61 (d, $J = 16$ Hz, 1 H), 4.71 (dd, $J = 16, 3$ Hz, 1 H), 4.84 (dd, $J = 16, 3$ Hz, 1 H), 6.08 (dd, $J = 6, 1$ Hz, 1 H), 6.56 (dd, $J = 6, 1$ Hz, 1 H), 6.77 (dd, $J = 6, 1$ Hz, 1 H), 7.10 (d, $J = 6$ Hz, 1 H), 7.07 - 7.38 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS) (apparent peaks) $\delta = 45.14$, 45.23 (d, $J = 9$ Hz), 72.43 (dq, $J = 30, 26$ Hz), 122.59 (q, $J = 281$ Hz), 125.49 (d, $J = 10$ Hz), 127.32, 127.87, 128.07, 128.65, 128.89, 130.81, 132.92 (d, $J = 8$ Hz), 135.84, 136.11 (d, $J = 275$ Hz), 137.68, 143.08, 169.14 (d, $J = 2$ Hz), 170.71; ^{19}F NMR (85 MHz, $CDCl_3$, 25 °C, $CFCl_3$) $\delta = -69.3$ (d, $J = 20$ Hz, 3F), -121.1 (q, $J = 20$ Hz, IF); IR (KBr): $\nu = 1711$ (C=O), 1670 (C=C) cm^{-1}; EI-MS *m/z* (%): 443 (7) $[M^+ + 1]$, 442 (26) $[M^+]$, 351 (22) $[M^+ - C_6H_5CH_2]$, 91 (100) $[C_6H_5CH_2^+]$.

References and Notes

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(4) We presented this product with a wrongly assigned structure such as stereoisomeric mixture of [2 + 2]cyclodimers of difluoroolefin **2a** in the following international chemical conferences: (a) 15th International Symposium on Fluorine Chemistry, Vancouver, 1997 (abstract: O(4)C-8). (b) 16th International Congress of Heterocyclic Chemistry, Bozeman, 1997 (abstract: POII-202).

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(6) Dimerization and Michael addition of trifluoroangelicalactone will be reported elsewhere.

(7) Two enantiomeric pairs of epimers (5'-*R*,5"-*R*/5'-*S*,5"-*S* and 5'-*R*,5"-*S*/5'-*S*,5"-*R*) can be considered for the sturucture of trimeric products **7**. The ^1H NMR sprectra of **7b** and **7c** revealed the products are single enatiomer pairs although the rigorous structures could not be determined.

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