Lactonizations of Carboxylic Acid-substituted 3-
Fluorodihydropyridines with Electrophiles: Peculiar Behaviour of F⁺

Henri Rudler,* Andée Parlier,* Louis Hamon,* Patrick Herson* and Jean-Claude Daran⁶

Experimental section

General information. Reactions were run under an inert atmosphere. All glassware was dried into oven prior to use. Dichloromethane and CH₃CN were distillated on P₂O₅. Column chromatography was performed using 70-230 mesh silica. Melting points were obtained on a Koffler bank and are uncorrected. Nuclear magnetic resonance spectra were recorded on Bruker AV 400 spectrometer. Chemical shifts for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.25 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ¹⁹F NMR spectra are recorded in parts per million from trifluorotrimethylsilane using trifluorotoluene resonance as the internal standard. Chemical shifts for ¹³C are recorded in parts per million from tetramethylsilane using the central peak of CDCl₃ (77.1 ppm) as the internal standard. Analysis were performed by the Service de Microanalyse I.C.S.N.- C.N.R.S.

2-(3-fluoro-1-(methoxycarbonyl)-1,4-dihydropyridin-4-yl)-2-methylpropanoic acid 4a.

To a dry 100 mL round-bottom flask purged with argon was added 3-fluoropyridine (0.65mL, 7.5mmol), and bis(trimethylsilyl)ketene acetal 1a (2.26mL, 9.75 mmol). Dry dichloromethane (40mL) was added and the mixture was cooled to 0°C. A solution of methylchloroformate (1.21mL, 15.8mmol) in dichloromethane (5mL) was added dropwise with a dropping funnel. The mixture was allowed to warm up to room temperature and stirred for 12 hours. After evaporation of the solvent under reduced pressure, the crude residue was chromatographed on silica gel. Elution with ethyl acetate / petroleum ether give 4a as a white solid, Mp= 122 °C (1.64 g, 90%). 2 rotamers. ¹H NMR (400MHz, CDCl₃) δ: 7.04 and 6.92 (d, J=10Hz, 1H, H₂), 6.91 and 6.80 (d, J=8Hz, 1H, H⁶), 4.96 and 4.89 (bs, 1H , H⁵), 3.80 (s, 3H, OCH₃), 3.78 (t, J=4Hz, 1H, H⁴), 1.18 (s, 6H, 2CH₃). ¹³C NMR (100MHz, CDCl₃) δ: 182.30 (COOH), 151.60 and 151.29 (NCOOCH₃), 149.7 and 147.2 (d, J=250Hz, C³), 124.58 and 124.21 (C⁶), 110.19 and 109.7 (d, J=44Hz, C²), 105.13 and 104.94 (d, J=13Hz, C⁵), 53.89
and 53.83 (OCH₃), 46.19 (C¹'), 43.55 and 43.19 (d, J=21Hz, C⁴), 22.17 and 21.84, 21.40 and 21.22 (2 CH₃). ¹⁹F NMR (376MHz, CDCl₃) δ: -134.4 and -133.9 (bs).

1-(3-fluoro-1-(methoxycarbonyl)-1,4-dihydropyridin-4-yl) cyclohexanecarboxylicacid 4b.

Same procedure as above was used with bis(trimethylsilyl)ketene acetal 1b (2.65mL, 9.75 mmol). 4b was obtained as a white solid, Mp=133°C (1.8g, 85%). 2 rotamers. ¹H NMR (400MHz, CDCl₃) δ: 7.0 and 6.95 (d, J=5Hz, 1H, H²), 6.91 and 6.81 (d, J=6Hz, 1H, H⁶), 4.97 and 4.87 (bs, 1H, H⁵), 3.8 (s, 3H, OCH₃) 3.57 (t, J=5.5Hz, 1H, H⁴), 1.10-2.10 (m, 10H, 5CH₂). ¹³C NMR (100MHz, CDCl₃) δ: 181.33 (COOH), 151.62 and 151.30 (NCOOCH₃), 148.2 and 147.7 (d, J=249Hz, C⁶), 124.68 and 124.28 (C⁵), 110.30 and 110.16 (d, J=44Hz, C⁵), 53.82 (OCH₃), 52.08 (C¹'), 45.05 (d, J=21Hz, C⁴), 30.39, 30.16, 28.78, 25.46, 23.66 (5CH₂). ¹⁹F NMR (376MHz, CDCl₃) δ: -132.4 and -131.8 (bs).

Methyl 6-fluoro-4,4-dimethyl-3oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-carboxylate 6a

To a solution of dihydropyridine 4a (443 mg, 1.823 mmol) in dry CH₂Cl₂, was added dropwise with syringe a solution of HCl in diethylether (2 mL, 1M, 2.01 mmol). The mixture was stirred during 3 days at room temperature. A saturated solution of NaHCO₃ (10 mL) was added. The mixture was decanted and water phase extracted twice with CHCl₃, organic phase washed with brine and dried over Na₂SO₄ and finally concentrated under reduced pressure. 6a was obtained as a white solid Mp= 106 °C (281 mg, 63%). 2 rotamers. ¹H NMR (400MHz, CDCl₃) δ: 6.92 and 6.79 (d, J=9Hz, 1H, H⁷), 6.41 and 6.26 (bs, 1H, H¹), 3.82 and 3.80 (s, 3H, OMe), 2.58 (m, 1H, H⁸), 2.43 (d, J=12Hz, 1H, H⁵), 1.96 (m, 1H , H⁹),1.40 ,1.39 and 1.37 (s, 6H, 2CH₃). ¹³C NMR (100MHz, CDCl₃) δ: 174.77 (C⁵), 152.25 and 151.95 (NCO), 148.38 and 147.45 (d, J=250Hz, C⁶), 107.45 (d, J=42Hz, C⁷), 78.73 and 78.49 (C¹'), 54.03 and 53.90 (OCH₃), 42.81 and 42.74 (C⁴), 38.28 and 38.17 (d, J=22Hz, C⁵), 27.20, 27.07, 25.26, (Me), 23.77 (d, JCF=6Hz, C⁹). ¹⁹F NMR (376MHz, CDCl₃) δ: -128.21 and -128.98 (bs).

Same procedure as above with dihydropyridine $4b$ (566 mg, 2mmol) and HCl solution (2.2 mL, 1M, 2.2mmol). $6b$ was obtained as a white solid $\text{Mp} = 128^\circ\text{C}$ (347 mg, 61%). 2 rotamers. $^1\text{H NMR (400MHz, CDCl}_3\text{)} \delta$: 6.91 and 6.79 (d, $J_{HF}=10\text{Hz}, 1\text{H, H}^7$), 6.34 and 6.19 (bs, 1H, H$^1$), 3.79 (s, 3H, OMe), 2.92 (d, $J_{HF}=12\text{Hz}, 1\text{H, H}^5$), 2.53 (bs, 1H , H$^9$), 2.15-1.40 (m, 11H, 5CH$_2$ and H$^9$). $^{13}\text{C NMR (100MHz, CDCl}_3\text{)} \delta$: 174.56 (C$^3$), 152.17 and 151.94 (NCO), 149.65 and 148.81 (d, $J_{CF}=250\text{Hz, C}^6$), 107.44 (d, $J_{CF}=41\text{Hz, C}^7$), 77.85 and 77.62 (C$^1$), 53.89 and 53.77 (OCH$_3$), 46.49 (C$^4$), 33.54 (CH$_2$), 32.62 (CH$_2$), 32.37 and 31.25 (d, $J_{CF}=21\text{Hz, C}^5$), 25.29 (CH$_2$), 23.39 and 23.02 (d, $J_{CF}=6\text{Hz, C}^9$), 21.20 (CH$_2$), 20.74(CH$_2$). $^{19}\text{F NMR (376MHz, CDCl}_3\text{)} \delta$: -129.39 and -130.15 (bs).


To a solution of dihydropyridine $4b$ (237 mg, 0.84 mmol), in dry CHCl$_3$ (70 mL), was added CuBr$_2$ (1.123g, 5.02 mmol) and Al$_2$O$_3$ (512 mg, 5.02 mmol). The mixture was heated to 60-65°C during 17 h. After filtration through celite, and evaporation of the solvent under reduced pressure, the crude was chromatographed on silica gel. $7b$ was obtained as a yellow solid $\text{Mp} = 154^\circ\text{C}$ (293 mg, 98%). 2 rotamers. $^1\text{H NMR (400MHz, CDCl}_3\text{)} \delta$: 7.01 and 6.88 (d, $J_{HF}=9\text{Hz, 1H, H}^7$), 6.27 and 6.10 (bs, 1H, H$^1$), 4.79 (m, 1H , H$^9$), 3.84 (s, 3H, OMe), 3.11 (d, $J_{HF}=11\text{Hz, 1H, H}^5$), 2.13-1.26 (m, 10H, 5CH$_2$). $^{13}\text{C NMR (100MHz, CDCl}_3\text{)} \delta$: 172.43 (C$^3$), 152.44 and 152.06 (NCO), 146.52 and 145.80 (d, $J_{CF}=250\text{Hz, C}^6$), 107.11 and 107.02 (d, $J_{CF}=40\text{Hz, C}^7$), 79.91 and 79.50 (C$^1$), 54.29 and 54.18 (OCH$_3$), 49.40 (C$^4$), 41.89 and 41.48 (d, $J_{CF}=21\text{Hz, C}^5$), 35.87 and 35.52 (d, $J_{CF}=7\text{Hz, C}^9$), 33.74, 33.64, 25.09, 21.21, 20.53 (5CH$_2$). $^{19}\text{F NMR (376MHz, CDCl}_3\text{)} \delta$: -132.6 and -133.3 (bs).


To a solution of dihydropyridine $4b$ (403 mg, 1.424 mmol) and I$_2$ (380 mg, 1.495 mmol) in dry CH$_2$Cl$_2$, was added a saturated solution of NaHCO$_3$ (10 mL). The mixture was stirred at room temperature during 17h then transferred into separating funnel and decanted. Aqueous phase was extracted 3 times with CH$_2$Cl$_2$. The organic phase was washed with a solution of NaHSO$_3$ then with water, dried on Na$_2$SO$_4$ and concentrated under reduced pressure. $8b$ was obtained as a white solid $\text{Mp} = 145^\circ\text{C}$ (decomp.) (477 mg, 82%). 2 rotamers. $^1\text{H NMR (400MHz, CDCl}_3\text{)} \delta$: 7.0 and 6.87 (d, $J_{HF}=10\text{Hz, 1H, H}^7$), 6.29 and 6.13 (bs, 1H, H$^1$), 4.93
(bs, 1H, H^9), 3.85 (s, 3H, OMe), 3.06 (d, J_HF=11Hz, 1H, H^5), 2.12-1.40 (m, 10H, 5CH_2). ^{13}C\text{NMR (100MHz, CDCl}_3\text{)} \delta: 172.42 (C^3), 152.40 and 152.04 (NCO), 146.52 and 145.80 (d, J_CF=250 Hz, C^6), 107.09 (d, J_CF=40 Hz, C^7), 81.01 and 80.46 (C^1), 54.35 and 54.24 (OCH_3), 49.89 and 49.85 (C^4), 43.26 and 43.12 (d, J_CF=21Hz, C^5), 33.73, 33.29, 25.16, 21.33, 20.66 (5CH_2), 11.04 and 10.73 (d, J=7Hz, C^9). ^{19}F\text{NMR (376MHz, CDCl}_3\text{)} \delta: -131.8 ppm and -132.5 ppm (bs).

Analysis Calcd for C_{14}H_{17}FNO_4: C, 41.09; H, 4.19; N, 3.42. Found: C, 41.57; H, 4.22; N, 3.34.


To a suspension of metachloroperbenzoic acid (414 mg, 2.4 mmol) in dry CH_2Cl_2 (10 mL) cooled to -5°C, was added a solution of dihydropyridine 4b (566 mg, 2 mmol) in CH_2Cl_2 (10 mL). After 10 mn, the ice bath was taken off and the mixture allowed to stir at room temperature during 3 h. NaOH solution (10%, 10 mL) was added, the mixture was transferred into a separating funnel and decanted. Aqueous phase was extracted 3 times with CHCl_3. The organic phase was washed with water, and dried over Na_2SO_4. Solvent was removed under reduced pressure. The crude was chromatographed on silica gel. Lactone 6b (57 mg, 10%) eluted first then 9b obtained as a white solid Mp = 197°C (162 mg, 27%). 2 rotamers. ^1H\text{NMR (400MHz, CDCl}_3\text{)} \delta: 7.0 and 6.86 (d, J=9Hz, 1H, H^7), 6.10 and 5.93 (bs, 1H, H^5), 4.48 and 4.44 (bs, 1H, H^9), 3.78 (s, 3H, OMe), 2.95 (d, J=10.5 Hz, 1H, H^5), 2.00-1.21 (m, 10H, 5CH_2). ^{13}C\text{NMR (100MHz, CDCl}_3\text{)} \delta: 173.66 (C^3), 153.05 and 152.74 (NCO), 146.95 and 145.25 (d, J=250 Hz, C^6), 107.57 (d, J=40 Hz, C^7), 79.31 and 79.04 (C^1), 59.44 and 58.91 (C^9), 54.26 and 54.16 (OCH_3), 47.61 (C^4), 40.25 (bs, C^5), 33.86, 33.22, 25.27, 21.27, 20.59 (5CH_2). ^{19}F\text{NMR (376MHz, CDCl}_3\text{)} \delta: -131.8 ppm and -132.5 ppm (bs).

Analysis Calcd for C_{14}H_{18}FNO_5: C, 56.18; H, 6.06; N, 4.68. Found: C, 56.44; H, 5.85; N, 4.59.

Methyl 9-fluoro-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate 10a.

To a solution of dihydropyridine 2a (497 mg, 2.21 mmol) in CH_3CN (35 ml) was added NaHCO_3 (264 mg, 3.14 mmol), then selectfluor (870 mg, 2.46 mmol). The mixture was stirred during 2 days to room temperature. Cold water was added (10 mL), the mixture was transferred into a separating funnel and decanted. The aqueous phase was extracted 3 times with CHCl_3. The organic phase was washed twice with a dilute solution of HCl, once with...
water, and dried over Na₂SO₄. Solvent was removed under reduced pressure. 10a was obtained as a white solid Mp = 116°C (371 mg, 69%). 2 rotamers. ¹H NMR (400MHz, CDCl₃) δ: 6.96 and 6.82 (d, J₇H=8Hz, 1H, H⁷), 6.42 and 6.26 (bs, 1H, H¹), 5.40 and 5.37 (d, J=48Hz, 1H , H⁹), 5.09 and 5.00 (t, J=8Hz, H⁶), 3.83 (s, 3H, OMe), 2.45 (d, J₉H=8Hz, 1H, H⁵), 1.42 (s, 3H, Me), 1.36 (s, 3H, Me). ¹³C NMR (100MHz, CDCl₃) δ: 174.16 (C³), 152.94 and 152.66 (NCO), 122.46 and 122.37 (C⁷), 103.64 and 103.28 (C⁶), 78.54 (d, J₉C=197 Hz, C⁹), 78.31 (d, J₉C=27Hz, C¹), 54.02 (OCH₃), 44.52 and 44.42 (C⁴), 39.57 (t, J=20Hz, C⁵), 27.44 and 27.32 (Me), 25.99 (Me). ¹⁹F NMR (376MHz, CDCl₃) δ: -198.10 and -199.3 (dd, J=48 and J=8Hz). Analysis Calcd for C₁₁H₁₄FNO₄: C, 54.32; H, 5.80; N, 5.76. Found: C, 54.21; H, 5.83; N, 5.56.


Same procedure as above with dihydropyridine 2b (589 mg, 2.22 mmol), NaHCO₃ (261 mg, 3.11 mmol) and select fluor (864 mg, 2.44 mmol). 10b was obtained as a white solid Mp=141°C (484 mg, 77%). 2 rotamers. ¹H NMR (400MHz, CDCl₃) δ: 6.98 and 6.84 (d, J₇H=8Hz, 1H, H⁷), 6.39 and 6.23 (bs, 1H, H¹), 5.34 and 5.31 (d, J = 48Hz, 1H , H⁹), 5.03 and 4.97 (bs, 1H, H⁶), 3.82 (s, 3H, OMe), 2.88 (bs, 1H, H⁵), 2.00-1.23 (m, 10H, 5CH₂). ¹³C NMR (100MHz, CDCl₃) δ: 173.95 (C³), 152.95 and 152.69 (NCO), 122.82 and 122.71 (C⁷), 102.93 and 102.58 (C⁶), 78.74 and 78.61 (d, J₉C=185Hz, C⁹), 77.41 and 77.11 (t, J₉C=27Hz, C¹), 53.98 (OCH₃), 48.35 and 48.26 (C⁴), 33.81 (CH₂), 33.61 and 33.35 (d, J₉C=22Hz, C⁵), 32.88, 25.16, 21.29, 20.56 (4CH₂). ¹⁹F NMR (376MHz, CDCl₃) δ: -198.8 and -198.9 (d, J=48Hz). Analysis Calcd for C₁₄H₁₈FNO₄: C, 59.35; H, 6.40; N, 4.94. Found: C, 58.92; H, 6.22; N, 4.64.


Same procedure as above with dihydropyridine 4b (566 mg, 2 mmol), NaHCO₃ (201.6 mg, 2.4 mmol) and select fluor (849.6 mg, 2.4 mmol). The crude was chromatographed on silica gel, 11b was obtained as a white solid Mp = 110°C (242 mg, 40%). 2 rotamers. ¹H NMR (400MHz, CDCl₃) δ: 6.88 and 6.75 (d, J=8Hz, 1H, H⁷), 6.20 and 6.03 (d, J=4Hz, 1H, H¹), 5.04 (m, 1H, H⁹), 3.84 (s, 3H, OMe), 3.00 (m, 1H, H⁵), 2.20-1.00 (m, 10H, 5CH₂). ¹³C NMR
(100MHz, CDCl₃) δ: 172.67 (C³), 152.23 and 151.98 (NCO), 122.64 and 122.46 (C⁷), 115.97 (t, J=248Hz, C⁹), 103.22 (C⁶), 79.02 and 78.31 (d, J=34Hz, C¹), 54.16 (OMe), 48.44 (C⁴), 36.10 (m, C⁵), 35.98, 35.79, 35.60, 34.89, 34.78, 34.28, 24.98, 20.90, 20.79 (5CH₂).

19F NMR (376MHz, CDCl₃) δ: -112.1 (d, J=251Hz, F₁), -117.2 (d, J=251Hz, F₂).

Analysis: Calcd for C₁₄H₁₇F₂NO₄: C, 55.81; H, 5.69; N, 4.65. Found: C, 55.78; H, 5.71; N, 4.59.

Then 12b as a white solid too Mp=140°C (190 mg, 32%). 2 rotamers.

1H NMR (400MHz, CDCl₃) δ: 7.03 and 6.90 (d, J=9Hz, 1H, H⁷), 6.33 and 6.17 (bs, 1H, H¹), 5.31 (d, J= 47Hz, 1H, H⁵), 3.83 (s, 3H, OMe), 3.18 (t, J=9Hz, 1H, H⁵), 2.10-1.35 (m, 10H, 5CH₂).

13C NMR (100MHz, CDCl₃) δ: 172.62 (C³), 152.59 and 152.19 (NCO), 146.09 and 145.39 (d, J=247Hz, C⁶), 107.61 and 107.28 (d, J=40Hz, C⁷), 78.32 and 77.95 (dd, J=200 and J=6Hz, C⁹), 76.70 and 76.44 (t, J= 26Hz, C¹) 54.18 and 54.13 (OMe), 47.77 (C⁴), 38.35 and 37.98 (d, J=17Hz, C⁵), 33.98, 33.90, 33.07, 25.15, 21.26, 20.52 (5CH₂).

19F NMR (376MHz, CDCl₃) δ: -134.2 and -134.8 (bs, F⁶), -198.4 and 198.7 (dd, J=47 and J= 7Hz, F⁹).

Analysis: Calcd for C₁₄H₁₈FNO₄: C, 55.81; H, 5.69; N, 4.65. Found: C, 55.69; H, 5.75; N, 4.51.