Supplementary Material (ESI) for Chemical Communications

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

Henri Rudler,*[a] Andrée Parlier,[a] Louis Hamon,[a] Patrick Herson[a] and Jean-Claude Daran[b]

Experimental section

General information. Reactions were run under an inert atmosphere. All glassware was dried into oven prior to use. Dichloromethane and CH_3CN were distillated on P_2O_5. 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 ^{19}F NMR spectra are recorded in parts per million from fluorotrichloromethane using trifluorotoluene resonance as the internal standard. Chemical shifts for ^{13}C are recorded in parts per million from tetramethylsilane using the central peak of $CDCl_3$ (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 ethylacetate / petroleum ether give **4a** as a white solid, Mp= 122 °C (1.64 g, 90%). 2 rotamers. **^1H NMR (400MHz, $CDCl_3$)** δ: 7.04 and 6.92 (d, J=10Hz, 1H, H^2), 6.91 and 6.80 (d, J=8Hz, 1H, H^6), 4.96 and 4.89 (bs, 1H , H^5), 3.80 (s, 3H, OCH_3), 3.78 (t, J=4Hz, 1H, H^4), 1.18 (s, 6H, $2CH_3$). **^{13}C NMR (100MHz, $CDCl_3$)** δ: 182.30 (COOH), 151.60 and 151.29 ($NCOOCH_3$), 149.7 and 147.2 (d, J=250Hz, C^3), 124.58 and 124.21 (C^6), 110.19 and 109.7 (d, J=44Hz, C^2), 105.13 and 104.94 (d, J=13Hz, C^5), 53.89

and 53.83 (OCH_3), 46.19 ($C^{1'}$), 43.55 and 43.19 (d, J=21Hz, C^4), 22.17 and 21.84, 21.40 and 21.22 (2 CH_3). **^{19}F NMR (376MHz, $CDCl_3$)** 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. **^{1}H NMR (400MHz, $CDCl_3$)** δ: 7.0 and 6.95 (d, J=5Hz, 1H, H^2), 6.91 and 6.81 (d, J=6Hz, 1H, H^6), 4.97 and 4.87 (bs, 1H, H^5), 3.8 (s, 3H, OCH_3) 3.57 (t, J=5.5Hz, 1H, H^4), 1.10-2.10 (m, 10H, $5CH_2$). **^{13}C NMR (100MHz, $CDCl_3$)** δ: 181.33 (COOH), 151.62 and 151.30 ($NCOOCH_3$), 148.2 and 147.7 (d, J=249Hz, C^3), 124.68 and 124.28 (C^6), 110.30 and 110.16 (d, J=44Hz, C^2), 104.9 and 104.7 (d, J=14Hz, C^5), 53,82 (OCH_3), 52,08 ($C^{1'}$), 45.05 (d, J=21Hz, C^4), 30.39, 30.16, 28.78, 25.46, 23.66 ($5CH_2$). **^{19}F NMR (376MHz, $CDCl_3$)** 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 CH_2Cl_2, was added dropwise with syringe a solution of HCl in diethylether (2 mL, 1M, 2.01 mmol). The mixture was strirred during 3 days at room temperature. A saturated solution of $NaHCO_3$ (10 mL) was added. The mixture was decanted and water phase extracted twice with $CHCl_3$, organic phase washed with brine and dried over Na_2SO_4 and finaly concentrated under reduced pressure. **6a** was obtained as a white solid Mp= 106 °C (281 mg, 63%). 2 rotamers. **^{1}H NMR (400MHz, $CDCl_3$)** δ: 6.92 and 6.79 (d, J=9Hz, 1H, H^7), 6.41 and 6.26 (bs, 1H, H^1), 3.82 and 3.80 (s, 3H, OMe), 2.58 (m, 1H, H^9), 2.43 (d, J=12Hz, 1H, H^5), 1.96 (m, 1H , H^9),1.40 ,1.39 and 1.37 (s, 6H, $2CH_3$). **^{13}C NMR (100MHz, $CDCl_3$)** δ: 174.77 (C^3), 152.25 and 151.95 (NCO), 148.38 and 147.45 (d, J=250Hz, C^6), 107.45 (d, J=42Hz, C^7), 78.73 and 78.49 (C^1), 54.03 and 53.90 (OCH_3), 42.81 and 42.74 (C^4), 38.28 and 38.17 (d, J=22Hz, C^5), 27.20, 27.07, 25.26, (Me), 23.77 (d, J_{CF}=6Hz, C^9). **^{19}F NMR (376MHz, $CDCl_3$)** δ: -128.21 and -128.98 (bs).

Methyl 6-fluoro-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non[6]ene-4,1'-cyclohexane]-8-carboxylate 6b.

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 Mp = 128°C (347 mg, 61%). 2 rotamers. **^{1}H NMR (400MHz, $CDCl_3$)** δ: 6.91 and 6.79 (d, J_{HF}=10Hz, 1H, H^7), 6.34 and 6.19 (bs, 1H, H^1), 3.79 (s, 3H, OMe), 2.92 (d, J_{HF}=12Hz, 1H, H^5), 2.53 (bs, 1H , H^9), 2.15-1.40 (m, 11H, $5CH_2$ and H^9). **^{13}C NMR (100MHz, $CDCl_3$)** δ: 174.56 (C^3), 152.17 and 151.94 (NCO), 149.65 and 148.81 (d, J_{CF}=250Hz, C^6), 107.44 (d, J_{CF}=41Hz, 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}=21Hz, C^5), 25.29 (CH_2), 23.39 and 23.02 (d, J_{CF}=6Hz, C^9), 21.20 (CH_2), 20.74(CH_2). **^{19}F NMR (376MHz, $CDCl_3$)** δ: -129.39 and -130.15 (bs).

Methyl 9-bromo-6-fluoro-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non[6]ene-4,1'-cyclohexane]-8-carboxylate 7b.

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_2O_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 Mp =154°C (293 mg, 98%). 2 rotamers. **^{1}H NMR (400MHz, $CDCl_3$)** δ: 7.01 and 6.88 (d, J_{HF}=9Hz, 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}=11Hz, 1H, H^5), 2.13-1.26 (m, 10H, $5CH_2$). **^{13}C NMR (100MHz, $CDCl_3$)** δ: 172.43 (C^3), 152.44 and 152.06 (NCO), 146.52 and 145.80 (d, J_{CF}=250 Hz, C^6), 107.11and 107.02 (d, J_{CF}=40 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}=21Hz, C^5), 35.87 and 35.52 (d, J_{CF}=7Hz, C^9), 33.74, 33.64, 25.09, 21.21, 20.53 ($5CH_2$). **^{19}F NMR (376MHz, $CDCl_3$)** δ: -132.6 and -133.3 (bs).

Methyl 6-fluoro-9-iodo-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non[6]ene-4,1'-cyclohexane]-8-carboxylate 8b.

To a solution of dihydropyridine **4b** (403 mg, 1.424 mmol) and I_2 (380 mg, 1.495 mmol) in dry CH_2Cl_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_2Cl_2. The organic phase was washed with a solution of $NaHSO_3$ then with water, dried on Na_2SO_4 and concentrated under reduced pressure. **8b** was obtained as a white solid Mp = 145°C (decomp.) (477 mg, 82%). 2 rotamers. **^{1}H NMR (400MHz, $CDCl_3$)** δ: 7.0 and 6.87 (d, J_{HF}=10Hz, 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 NMR (100MHz, $CDCl_3$)** δ: 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 NMR (376MHz, $CDCl_3$)** δ: .**Analysis** Calcd for $C_{14}H_{17}FINO_4$: C, 41.09 ; H, 4.19 ; N, 3.42. Found : C, 41.57 ; H, 4.22 ; N, 3.34.

Methyl 6-fluoro-9-hydroxy-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non[6]ene-4,1'-cyclohexane]-8-carboxylate 9b.

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. **^{1}H NMR (400MHz, $CDCl_3$)** δ: 7.0 and 6.86 (d, J=9Hz, 1H, H^7), 6.10 and 5.93 (bs, 1H, H^1), 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 NMR (100MHz, $CDCl_3$)** δ: 173.66 (C^3), 153.05 and 152.74 (NCO), 130,92 and 128,80 (C^6) 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 NMR (376MHz, $CDCl_3$)** δ: -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-3oxo-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 Na_2SO_4. Solvent was removed under reduced pressure. **10a** was obtained as a white solid Mp = 116°C (371 mg, 69%). 2 rotamers. **^{1}H NMR (400MHz, $CDCl_3$)** δ: 6.96 and 6.82 (d, J_{HF}=8Hz, 1H, H^7), 6.42 and 6.26 (bs, 1H, H^1), 5.40 and 5.37 (d, J=48Hz, 1H , H^9), 5.09 and 5.00 (t, J=8Hz, H^6), 3.83 (s, 3H, OMe), 2.45 (d, J_{HF}=8Hz, 1H, H^5), 1.42 (s, 3H, Me), 1.36 (s, 3H, Me). **^{13}C NMR (100MHz, $CDCl_3$)** δ: 174.16 (C^3), 152.94 and 152.66 (NCO), 122.46 and 122.37 (C^7), 103.64 and 103.28 (C^6), 78.54 (d, J_{CF}=197 Hz, C^9), 78.31 (d, J_{CF}=27Hz, C^1), 54.02 (OCH_3), 44.52 and 44.42 (C^4), 39.57 (t, J=20Hz, C^5), 27.44 and 27.32 (Me), 25.99 (Me). **^{19}F NMR (376MHz, $CDCl_3$)** δ: -198.10 and -199.3 (dd, J=48 and J=8Hz). **Analysis** Calcd for $C_{11}H_{14}FNO_4$: C, 54.32; H, 5.80 ; N, 5.76. Found : C, 54.21 ; H, 5.83 ; N, 5.56.

Methyl 9-fluoro-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non[6]ene-4,1'-cyclohexane]-8-carboxylate 10b.

Same procedure as above with dihydropyridine **2b** (589 mg, 2.22 mmol), $NaHCO_3$ (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. **^{1}H NMR (400MHz, $CDCl_3$)** δ: 6.98 and 6.84 (d, J_{HF}=8Hz, 1H, H^7), 6.39 and 6.23 (bs, 1H, H^1), 5.34 and 5.31 (d, J = 48Hz, 1H , H^9), 5.03 and 4.97 (bs, 1H, H^6), 3.82 (s, 3H, OMe), 2.88 (bs, 1H, H^5), 2.00-1.23 (m, 10H, $5CH_2$). **^{13}C NMR (100MHz, $CDCl_3$)** δ: 173.95 (C^3), 152.95 and 152.69 (NCO), 122.82 and 122.71 (C^7), 102.93 and 102.58 (C^6), 78.74 and 78.61 (d, J_{CF}=185Hz, C^9), 77.41 and 77.11 (t, J_{CF}=27Hz, C^1), 53.98 (OCH_3), 48.35 and 48.26 (C^4), 33.81 (CH_2), 33.61 and 33.35 (d, J_{CF}=22Hz, C^5), 32.88, 25.16, 21.29, 20.56 ($4CH_2$). **^{19}F NMR (376MHz, $CDCl_3$)** δ: -198.8 and -198.9 (d, J=48Hz). **Analysis** Calcd for $C_{14}H_{18}FNO_4$: C, 59.35 ; H, 6.40 ; N, 4.94. Found : C, 58.92 ; H, 6.22 ; N, 4.64.

Methyl 9,9-difluoro-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non[6]ene-4,1'-cyclohexane]-8-carboxylat 11b and methyl 6,9-difluoro-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non[6]ene-4,1'-cyclohexane]-8-carboxylat 12b.

Same procedure as above with dihydropyridine **4b** (566 mg, 2 mmol), $NaHCO_3$ (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. **^{1}H NMR (400MHz, $CDCl_3$)** δ: 6.88 and 6.75 (d, J=8Hz, 1H, H^7), 6.20 and 6.03 (d, J=4Hz, 1H, H^1), 5.04 (m, 1H, H^6), 3.84 (s, 3H, OMe), 3.00 (m, 1H, H^5), 2.20-1.00 (m, 10H, $5CH_2$). **^{13}C NMR**

(100MHz, $CDCl_3$) δ: 172.67 (C^3), 152.23 and 151.98 (NCO), 122.64 and 122.46 (C^7), 115.97 (t, J=248Hz, C^9), 103.22 (C^6), 79.02 and 78.31 (d, J=34Hz, C^1), 54.16 (OMe), 48.44 (C^4), 36.10 (m, C^5), 35.98, 35.79, 35.60, 34.89, 34.78, 34.28, 24.98, 20.90, 20.79 ($5CH_2$). **^{19}F NMR (376MHz, $CDCl_3$)** δ: -112.1 (d, J_{FF}=251Hz, $F_1{}^9$), -117.2 (d, J=251Hz, $F_2{}^9$). **Analysis** Calcd for $C_{14}H_{17}F_2NO_4$: 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. **^{1}H NMR (400MHz, $CDCl_3$)** δ: 7.03 and 6.90 (d, J=9Hz, 1H, H^7), 6.33 and 6.17 (bs, 1H, H^1), 5.31 (d, J= 47Hz, 1H, H^9), 3.83 (s, 3H, OMe), 3.18 (t, J=9Hz, 1H, H^5), 2.10-1.35 (m, 10H, $5CH_2$). **^{13}C NMR (100MHz, $CDCl_3$)** δ: 172.62 (C^3), 152.59 and 152.19 (NCO), 146.09 and 145.39 (d, J=247Hz, C^6), 107.61 and 107.28 (d, J=40Hz, C^7), 78.32 and 77.95 (dd, J=200 and J=6Hz, C^9), 76.70 and 76.44 (t, J= 26Hz, C^1) 54.18 and 54.13 (OMe), 47.77 (C^4), 38.35 and 37.98 (d, J=17Hz, C^5), 33.98, 33.90, 33.07, 25.15, 21.26, 20.52 ($5CH_2$). **^{19}F NMR (376MHz, $CDCl_3$)** δ: -134.2 and -134.8 (bs, F^6), -198.4 and 198.7 (dd, J=47 and J= 7Hz, F^9). **Analysis** Calcd for $C_{14}H_{18}FNO_4$: C, 55.81; H, 5.69; N, 4.65. Found : C, 55.69 ; H, 5.75; N, 4.51.