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Lactonizations of carboxylic acid-substituted 3-fluorodihydropyridines with electrophiles: peculiar behaviour of F^+ †

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Received (in Cambridge, UK) 28th April 2008, Accepted 23rd May 2008
First published as an Advance Article on the web 8th July 2008
DOI: 10.1039/b807092j

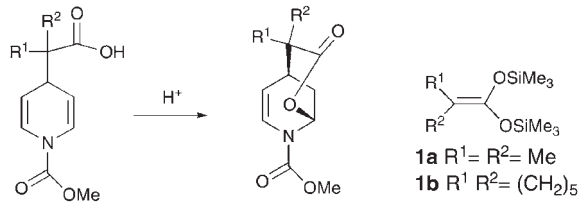
Published on 08 July 2008. Downloaded by New York University on 14/10/2014 04:41:28.

Whereas for 3-fluorodihydropyridine-substituted carboxylic acids electrophiles such as HCl, iodine, bromine and peracids discriminate the double bond lacking and that bearing fluorine, no such differentiation took place in the case of electrophilic fluorine since the formation of both mono and *gem*-difluorolactones took place.

The use of bis(TMS)ketene acetals **1** as dinucleophiles for the transformation of carbon–carbon double bonds either into γ- or δ-lactones has provided access to a large class of new polyheterocycles.[1] In the case of pyridines, these cycloadditions evolved *via* the formation of isolable 4-(1-carboxyalkyl)-dihydropyridines **2** which led very easily to stable δ-lactones **3** fused to tetrahydropyridines (Scheme 1).[2]

These ring-closure reactions were not only induced by protic acids but occurred also with electrophiles such as Br^+, I^+, HO^+, allowing thus to introduce various functionalities in β to the oxygen atom of the lactones. These results prompted us to consider the addition of electrophilic fluorine by the same means to get access to new fluorinated lactones.[3] It is indeed well established that the introduction of fluorine in organic compounds might not only lead to biologically active compounds but could possibly, in the case of biologically active compounds, deeply modify their activity.[4]

Several electrophilic fluorinating agents have been used in the literature for that purpose among which 1-chloromethyl 4-fluoro-1,4-diazoniabicyclo(2.2.2)octane bis(tetrafluoroborate) or Selectfluor™ **5** is now one of the most popular.[5] In the case of dihydropyridines, precedents for their oxidation with *N*-fluoropyridinium triflate and *N*-fluorodibenzenesulfonimide in the presence of external nucleophiles can be found in the literature: Lavilla *et al*. observed indeed the formation, in a stereocontrolled manner, of 3-fluorinated tetrahydropyridines.[6] We have therefore carried out such reactions both on *N*-carbomethoxy dihydropyridines **2** and on the 3-fluoro analogs **4** ($R^1 = R^2 = Me$; $R^1\ R^2 = (CH_2)_5$) which were

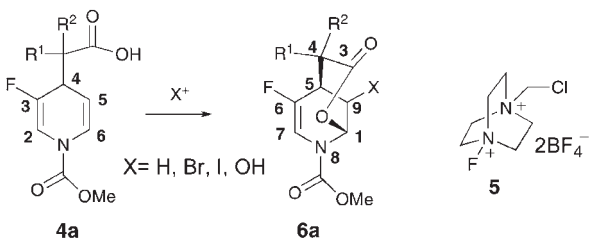


2 **3**

Scheme 1

prepared according to the published method and isolated in 85 to 90% yields.[1] The presence of fluorine in **4b** was confirmed by the ^{19}F NMR spectrum which disclosed two broad signals, at δ −131.8 and −132.4 ppm, whereas the ^{13}C NMR spectrum agreed with the suggested structure, C-3 giving rise to two doublets at δ 147.7 and 148.2 ppm (J = 249 Hz).[7] Treatment of **4b** with anhydrous HCl in diethyl ether led to a new compound the physical properties of which were consistent with those of the lactone **6b**. The ^{13}C NMR spectrum confirmed indeed the presence of a fluorine-substituted double bond as in **4b**, with two doublets at δ 149.65 and 148.81 ppm for C-6 (J = 250 Hz), at δ 107.44 ppm (d, J = 41 Hz) for C-7 and the typical signals for C-1 at δ 77.62 and 77.85 ppm (Scheme 2).

As far as other electrophiles are concerned,[1] we first examined the interaction of dihydropyridine **4b** with $CuBr_2$ on alumina, a selective source of electrophilic bromine.[1,7] This led indeed to an almost quantitative yield of a single compound **7b** (98%, mp 154 °C). Similarly, when the classical iodolactonization was applied to **4b**, a single lactone **8b** was obtained in 82% yield (white solid, mp 145 °C), the NMR data of which were in all respect comparable to those of **7b**, the signal for C-9 being highly shielded and appearing now at δ 10.73 and 11.04 ppm for the two



4a
4b

6a
6b
7b X=Br
8b X=I
9b X=OH

Scheme 2

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† Electronic supplementary information (ESI) available: Experimental section and physical data for **4a,b**, **6a,b**, **7b**, **8b**, **9b**, **10a,b**. CCDC reference numbers 668553 and 673543. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b807092j

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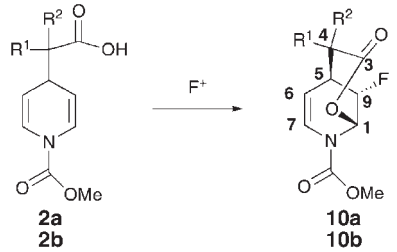
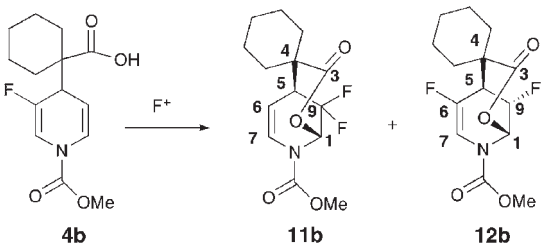


Scheme 3



Scheme 4

rotamers, as two doublets, $^{3}J_{CF}$ = 7 Hz. Finally, the interaction of **4b** with a slight excess of *m*-chloroperbenzoic acid led in a modest 27% yield to a crystalline compound, mp 197 °C, the physical data of which were in agreement with those of the expected hydroxylactone **9b**. Thus, all of these electrophiles reacted with the double bond lacking fluorine. However, the course of the reaction was different in the case of electrophilic fluorine. Thus, the reaction of **2a** in acetonitrile with a slight excess of Selectfluor™ in the presence of sodium hydrogen carbonate led to a single, new compound **10a** (white crystals, 69%, mp 116 °C), δCO, 174.16 ppm, containing a secondary fluorine atom according to its ^{1}H and ^{19}F NMR spectra with signals corresponding to two rotamers, at δ 5.40 and 5.37 ppm and at δ −198.10 and −199.3 ppm (J = 48 Hz) typical for *axially* oriented fluorines. Similarly, **2b** led to **10b** in 77% yield (white crystals, mp141 °C) (Scheme 3).

When however the same reaction was carried out on **4b**, two products were obtained (Scheme 4). To the less polar product (mp 110 °C, 40%) was assigned structure **11b** on the basis of its NMR data. Its ^{13}C NMR spectrum confirmed the existence of the lactone function, δCO, 172.67 ppm, of a disubstituted double bond C(6)═C(7) as in **10b**, and of a deshielded signal at δ 115.97 ppm as a triplet (J = 248 Hz), consistent with the presence of a geminal difluorinated carbon. This was also assessed by the ^{19}F NMR spectrum which disclosed two

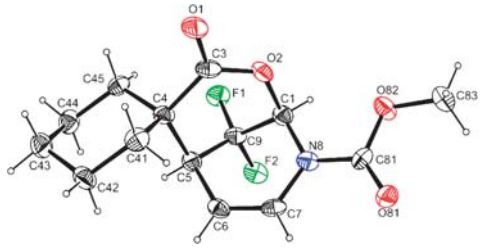


Fig. 1 X-Ray crystal structure of compound **11b**. Ellipsoids are drawn at the 30% probability level.

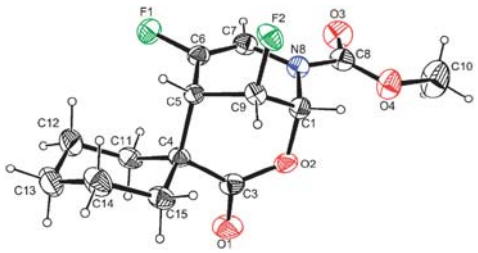


Fig. 2 X-Ray crystal structure of compound **12b**. Ellipsoids are drawn at the 30% probability level.

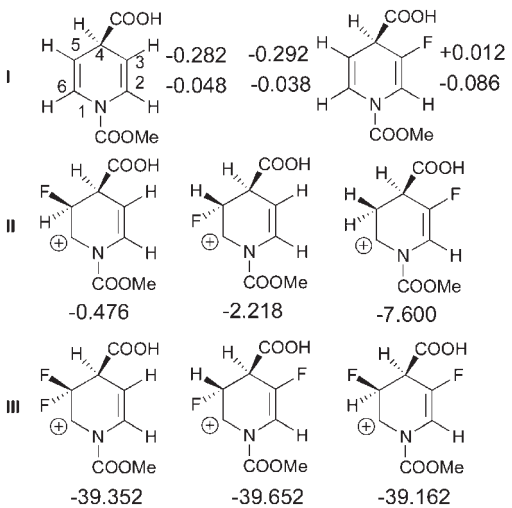
nonequivalent fluorine signals (two doublets) at −117.2 and −112.1 ppm, $^{2}J_{FF}$ = 248 Hz.‡

All of these data were secured by a single-crystal X-ray structure determination§ (Fig. 1).

To the second more polar product (mp 140 °C, 32%) was assigned structure **12b** on the basis of its NMR data. The presence of two types of fluorine atoms was confirmed by the ^{19}F NMR spectrum which disclosed indeed four signals for the two rotamers, at δ −134.8 and −134.2 ppm, as singlets (for F-6), and at δ −198.4 and −198.7 ppm, as doublets of doublets, J = 47 and 7 Hz, for F-9.‡ A crystal structure determination (Fig. 2) confirmed the regio- and stereochemistry of the reaction, the introduced fluorine being *trans*, *axial* with respect to the lactone bridge.§

Two points warrant therefore a comment: (a) *the stereochemical outcome* of the lactonization reaction of the dihydropyridines is the same whatever the nature of the halogen: all of the reactions led to *trans*, *diaxial* halolactones.[8a,c] Since fluorine decreases the electron density at the double bond, electrophilic additions are in general more difficult: it seems thus not surprising to observe only one of the two possible regioisomers with HCl and typical other electrophiles.[8d,e] This result agrees also with the calculated charge distributions (Scheme 5 (I)).[9]

Moreover, if one considers the relative enthalpies of the transition states, it appears that protonation of the fluorine-free double bond is favoured by 7.1 (for the *trans*-H) and by 5.5 kcal mol^{-1} (for the *cis*-H) over the fluorine-substituted double bond. (Scheme 5 (II)). Similarly, the addition of F^{+} to dihydropyridine



Scheme 5

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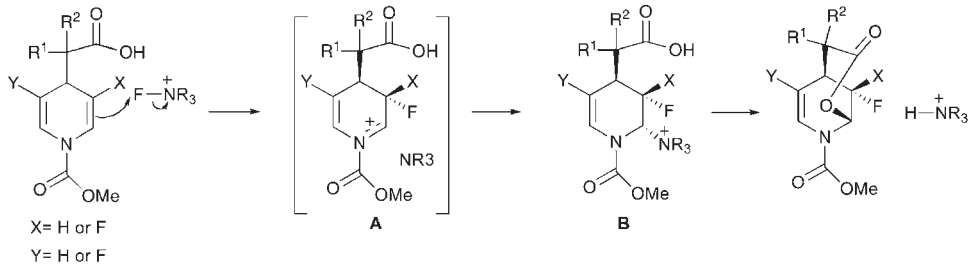

Scheme 6

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2 should also lead to the *trans* fluorolactone. Let's now examine the interaction of Selectfluor™ with **4**. It has been established that polarized double bonds react with Selectfluor™, according to a two stage process.[8b] Accordingly, a nucleophilic addition of the double bond to fluorine with cleavage of the fluorine–nitrogen bond, neutralization of the developing positive charge on the α-carbon in **A** by NR_3 (NR_3 = TEDA–$CH_2Cl^+BF_4^-$), would first give *syn* addition products **B**. In the second step, an intramolecular substitution might lead to the observed lactones (Scheme 6).

The formation of the *gem*-difluoro lactone **11** is reminiscent of the transformation of 2-fluoro enol ethers into *gem*-difluoro compounds.[10,11] Therefore, competition between the formation of **11** and **12** might indeed exist. According to calculations (Scheme 5 (III)) the enthalpies of formation of the 3-*gem* difluoro cation and the 3,5-difluoro-substituted intermediate carbocationic species are roughly the same. Therefore, the ratio of **11** to **12** should depend on the relative rates of transformation of the last intermediate **B**. Since in both intermediates (X = F, X = H) the introduced fluorine is axial, *cis* with respect to NR_3^+, a similar stabilizing effect might be observed,[12] and thus a similar rate of the intramolecular lactonization of both intermediates **B** (X = H and X = F), the influence of either one or two fluorine atoms on the α-carbon being almost the same.

Our current efforts include expanding the scope of these reactions to polyfluorinated dihydropyridines, getting a deeper insight into the mechanism of these transformations, and achieving enantioselective lactonizations.

Notes and references

‡ **11b**: White solid, mp 110 °C, 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 and 6.75 (d, J = 8 Hz, 1H, H^7), 6.20 and 6.03 (d, J = 4 Hz, 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 (100 MHz, $CDCl_3$) δ 172.67 (C^3), 152.23 and 151.98 (NCO), 122.64 and 122.46 (C^7), 115.97 (t, J = 248 Hz, C^9), 103.22 (C^6), 79.02 and 78.31 (d, J = 34 Hz, 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 (376 MHz, $CDCl_3$) δ −112.1 (d, J_{FF} = 251 Hz, F_1^9), −117.2 (d, J = 251 Hz, F_2^9). Analysis. Calc. 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%. **12b**: White solid, mp 140 °C, 32%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 and 6.90 (d, J = 9 Hz, 1H, H^7), 6.33 and 6.17 (br s, 1H, H^1), 5.31 (d, J = 47 Hz, 1H, H^9), 3.83 (s, 3H, OMe), 3.18 (t, J = 9 Hz, 1H, H^5), 2.10–1.35 (m, 10H, $5CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.62 (C^3), 152.59 and 152.19 (NCO), 146.09 and 145.39 (d, J = 247 Hz, C^6), 107.61 and 107.28 (d, J = 40 Hz, C^7), 78.32 and 77.95 (dd, J = 200 and J = 6 Hz, C^9), 76.70 and 76.44 (t, J = 26 Hz, C^1) 54.18 and 54.13 (OMe), 47.77 (C^4), 38.35 and 37.98 (d, J = 17 Hz, C^5), 33.98, 33.90, 33.07, 25.15, 21.26, 20.52 ($5CH_2$). ^{19}F NMR (376 MHz, $CDCl_3$) δ −134.2 and −134.8 (br s, F^6), −198.4 and 198.7 (dd, J = 47 and J = 7 Hz, F^9). Analysis. Calc. 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%.

§ *Crystal data* for **11b**: $C_{14}H_{17}F_2NO_4$, M = 301.29, orthorhombic, space group *Pbca*, a = 13.566(3), b = 10.620(2), c = 18.434(4) Å, V = 2655.9(9) Å^3, Z = 8, D_c = 1.507 g cm^{-3}, μ = 0.128 mm^{-1} (Mo-Kα, λ = 0.71073) T = 180 K, 5889 reflections collected; 1597 unique reflections (R_{int} = 0.149), $R1$, $wR2$ [$I > 2\sigma(I)$] = 0.0690, 0.1490, $R1$, $wR2$ (all data) = 0.1648, 0.2136. CCDC 668553. *Crystal data* for **12b**: $C_{14}H_{17}F_2NO_4$, M = 301.29, triclinic, space group $P\bar{1}$, a = 8.0326(8), b = 8.7779(11), c = 10.5283(10) Å, V = 693.44(14) Å^3, Z = 2, D_c = 1.443 g cm^{-3}, μ = 0.122 mm^{-1} (Mo-Kα, λ = 0.71073) T = 250 K, 12 253 reflections collected, 3300 unique reflections (R_{int} = 0.0493), $R1$, $wR2$ [$I > 2\sigma(I)$] = 0.0394, 0.0486 $R1$, $wR2$ (all data) = 0.0672, 0.0709. CCDC 673543.

1 (*a*) H. Rudler, B. Denise, Y. Xu, A. Parlier and J. Vaissermann, *Eur. J. Org. Chem.*, 2005, 3724–3744; (*b*) Y. Xu, H. Rudler, B. Denise, A. Parlier, P. Chaquin and P. Herson, *Tetrahedron Lett.*, 2006, **47**, 4541–4544.
2 For related transformations see, P. Langer, *Eur. J. Org. Chem.*, 2007, 2233–2238, and references therein.
3 L. F. Lourie, Y. A. Serguchev, G. V. Shevchenko, M. V. Ponomenko, A. N. Chernega, E. B. Rusanov and J. A. K. Howard, *J. Fluorine Chem.*, 2006, **127**, 377–385.
4 (*a*) W.-D. Meng and F.-L. Qing, *Curr. Top. Med. Chem.*, 2006, **6**, 1499–1528; (*b*) B. E. Smart, *J. Fluorine Chem.*, 2001, **109**, 3–11; (*c*) J. P. Bégué and D. Bonnet-Delpon, *Chimie Bioorganique et Médicinale du Fluor*, EDP Sciences/CNRS Eds, Paris, France, 2005; (*d*) R. P. Singh and J. M. Shree, *Acc. Chem. Res.*, 2004, **37**, 31–34; (*e*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319.
5 R. E. Banks, V. Murtagh and E. Tsiliopoulous, *J. Fluorine Chem.*, 1991, **52**, 389–401.
6 R. Lavilla, O. Coll, R. Kumar and J. Bosch, *J. Org. Chem.*, 1998, **63**, 2728–2730.
7 G. A. Rood, J. M. DeHaan and R. Zibuck, *Tetrahedron Lett.*, 1996, **37**, 157–158.
8 (*a*) R. D. Bach and H. F. Henneike, *J. Am. Chem. Soc.*, 1970, **92**, 5589–5602; (*b*) S. P. Vincent, M. D. Burkart, C.-Y. Tsai, Z. Zhang and C.-H. Wong, *J. Org. Chem.*, 1999, **64**, 5264–5279; (*c*) M. Albert, K. Dax and J. Ortner, *Tetrahedron*, 1998, **54**, 4839–4848; (*d*) R. N. Haszeldine, I-ud-D. Mir and A. E. Tipping, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2349–2353; (*e*) T. Tidwell, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 20–32.
9 M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. J. Jensen, S. Koseki, N. Matsunaya, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J. Comput. Chem.*, 1993, **14**, 1337–1363.
10 C. G. Francisco, C. C. Gonzalez, N. R. Paz and E. Suarez, *Org. Lett.*, 2003, **5**, 4171–4173.
11 M. J. Tozer and T. F. Herpin, *Tetrahedron*, 1996, **52**, 8619–8683.
12 N. E. J. Gooseman, D. O'Hagan, M. J. G. Peach, A. M. Z. Slawin, D. J. Tozer and R. J. Young, *Angew. Chem., Int. Ed.*, 2007, **46**, 5904–5908.

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