New approach to [*a*]-fused fluoroquinolones: the synthesis of 5-oxo-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinolines

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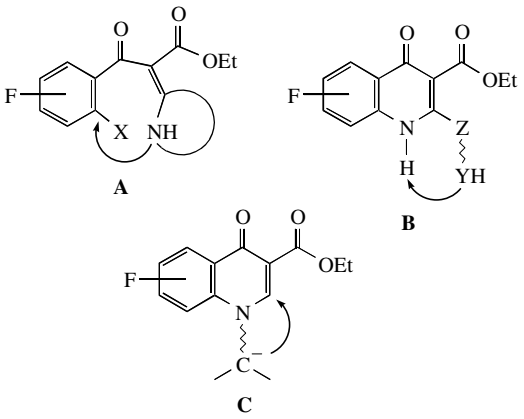
The reaction of *N*-(ethoxycarbonyl)methyl substituted ethyl 6,7-difluoro-, 6,7,8-trifluoro- and 5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinoline-3-carboxylates with methyl methacrylate results in the [3 + 2] adducts, hexahydropyrrolo[1,2-*a*]quinolones, which can be precursors of [*a*]-fused fluoroquinolones.

Among the tricyclic N_1–C_2 fused fluoroquinolones, compounds with excellent antimicrobial and other kinds of biological activity have been found.[1–3] A common strategy for the synthesis of this type of fused fluoroquinolones is based on condensation reactions of appropriately substituted heterocyclic synthons **A**–**C** (Scheme 1).



Scheme 1

In particular, pyrrolo[1,2-*a*]quinolones were obtained by the intramolecular condensation of cyclic derivatives of ethyl 3-amino-2-benzoyl acrylates **A**.[2] The second approach is based on the ring closure reactions of appropriate C_2-substituted quinolones **B**.[4] The first successful example of using the nucleophilic substitution of hydrogen at C_2 in fluoroquinolones **C** for the construction of [*a*]-fused tricyclic systems was performed through intramolecular addition of the Grignard reagent followed by oxidation of the intermediate σ-adduct.[5] Later we reported a new approach towards pyrazolo[1,5-*a*]quinolones *via* the [3 + 2] annelation resulting from the reaction of 1-amino-6-fluoro-4-quinolones with β-diketones.[6] A similar synthetic route to the same heterocyclic system of pyrazoloquinolones was developed by D. Barrett and co-workers *via* the tandem addition reaction of *N*-aminoquinolones with alkyl acrylates and other activated alkenes under basic condition.[7,8]

We report here the extension of this [3 + 2] annelation methodology based on tandem addition reactions. However, instead of the =N–NHR moiety, we used the CH-active *N*-(ethoxycarbonyl)methyl fragment in fluoroquinolones **1a**–**c** to generate nucleophilic species.

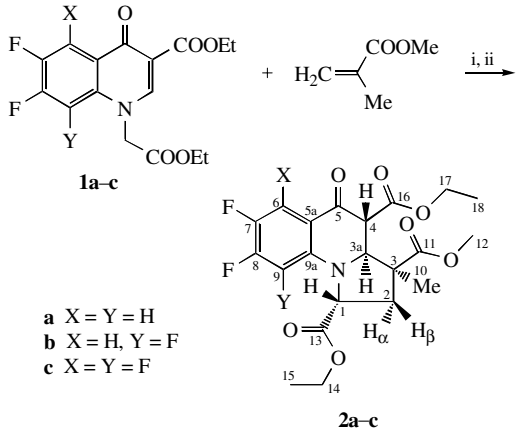
We found that the reaction of ethyl 6,7-difluoro-, 6,7,8-trifluoro- and 5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinoline-3-carboxylates **1a**–**c** with methyl methacrylate proceeds smoothly in an anhydrous DMF solution in the presence of sodium hydride and affords 5-oxo-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinolines **2a**–**c** in 50–61% yields (Scheme 2).

The ^{1}H NMR spectroscopy of reaction products **2a**–**c**† revealed that the mixtures of three stereomers were obtained in all cases in a ratio of approximately 2.5:1:trace. The major isomers were separated by silica gel column chromatography followed by crystallisation from hexane. The relative configuration of substituents in major diastereomers **2a** and **2b** was determined by NMR spectroscopy. The proton–proton coupling $^3J_{\text{H-4,H-3a}} \approx 14$ Hz for both compounds demonstrates the anti-periplanar (*trans*-) position of H-4 and H-3a, whereas the *cis*-arrangement of the pairs C-10 and H-3a, H-1 and H-2β is evident from the nuclear Overhauser effects (NOE, Scheme 3). Although the NOE for **2c** have not been measured, it is clear that the stereostructure of **2c** is just the same due to similarities of its spectral NMR characteristics to those of **2a**,**b**.

In conclusion, note that the reaction discovered provides an alternative route to fused pyrrolo[*a*]quinoline derivatives, the key intermediates for potential fluoroquinolone antibacterials. Moreover, compounds **2a**–**c** are of interest as novel representatives of the tricyclic fluoroquinolone system bearing the bridge-headed nitrogen atom and having structural similarities to natural alkaloids.

† The ^{1}H and ^{19}F NMR spectra were recorded in $CDCl_3$ solutions on Bruker WP-250 and Bruker WP-80-SY instruments (250 MHz for ^{1}H and 75 MHz for ^{19}F). Homonuclear ^{1}H–^{1}H Overhauser effects for compounds **2a**,**b** and the ^{13}C NMR spectrum of **2a** in $CDCl_3$ were obtained on a Bruker DRX-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). Mass spectra were recorded using a Varian MAT 311A spectrometer.

*1,4-Di(ethoxycarbonyl)-3-methoxycarbonyl-3-methyl-7,8-difluoro-5-oxo-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline* **2a**. A solution of ethyl *N*-(ethoxycarbonyl)methyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate **1a** (0.35 g, 1 mmol) in dry DMF (5 ml) was treated with sodium hydride (60% dispersion in oil) (50 mg, 1.2 mmol) and stirred for 15 min. Methyl methacrylate (0.33 ml, 3 mmol) was added to the reddish reaction mixture, which was allowed to stand at room temperature for 24 h (until **1a** disappeared and the solution became yellowish green). The reaction mixture was diluted with 10 ml of water; the pH of the solution was adjusted to 7.0 with 6% hydrochloric acid; and the contents were extracted with dichloromethane. The organic layers were washed with water, dried (Na_2SO_4) and evaporated. The oily residue was treated with diethyl ether–hexane to give **2a** (0.27 g, 61%) as a yellow powder. Major individual diastereoisomer **2a** was isolated as a colourless powder by silica gel column chromatography (eluent: hexane–ethyl acetate, 10:1) followed by crystallisation from hexane to yield 0.13 g (30%), mp 102–103 °C. ^{1}H NMR, δ: 1.21 (t, 3H, Me, ^3J 7.2 Hz), 1.33 (t, 3H, Me, ^3J 7.2 Hz), 1.35 (s, 3H, Me), 1.85 (dd, 1H, 2-H$_\alpha$, $^2J_{\text{2-H}_\alpha,\text{2-H}_\beta}$ 13.4 Hz, $^3J_{\text{2-H}_\alpha,\text{1-H}}$ 6.4 Hz), 3.08 (dd, 1H, 2-H$_\beta$, $^2J_{\text{2-H}_\beta,\text{2-H}_\alpha}$ 13.4 Hz, $^3J_{\text{2-H}_\beta,\text{1-H}}$ 9.0 Hz), 3.46 (d, 1H, 4-H, $^3J_{\text{4-H,3a-H}}$ 14.4 Hz), 3.70 (s, 3H, OMe), 4.19 (q, 2H, OCH_2, ^3J 7.2 Hz), 4.30 (q, 2H, OCH_2, ^3J 7.2 Hz), 4.38 (d, 1H, 3a-H, $^3J_{\text{3a-H,4-H}}$ 14.4 Hz), 4.48 (dd, 1H, 1-H, $^3J_{\text{1-H,2-H}_\alpha}$ 6.4 Hz, $^3J_{\text{1-H,2-H}_\beta}$ 9.0 Hz), 6.17 (dd, 1H, 9-H, $^3J_{\text{9-H,8-F}}$ 11.9 Hz, $^4J_{\text{9-H,7-F}}$ 6.1 Hz), 7.51 (dd, 1H, 6-H, $^3J_{\text{6-H,7-F}}$ 10.2 Hz, $^4J_{\text{6-H,8-F}}$ 9.0 Hz). ^{13}C NMR, δ: 14.0 (C-18), 14.02 (C-15), 21.94 (C-10), 40.51 (C-2, $^1J_{\text{2-C,2-H}}$ 139.0 and 133.6 Hz), 52.19 (C-12), 52.32 (C-3), 55.56 (C-4, $^1J_{\text{4-C,4-H}}$ 131.5 Hz), 59.37 (C-1, $^1J_{\text{1-C,1-H}}$ 150.7 Hz), 61.39 (C-17), 61.63 (C-14), 67.39 (C-3a, $^1J_{\text{C-3a,3a-H}}$ 145.9 Hz), 101.22 (C-9, $^1J_{\text{C-9,9-H}}$ 162.7 Hz), 113.12 (C-5a), 116.08 (C-6, $^1J_{\text{6-C,6-H}}$ 166.8 Hz), 143.46 (C-7, $^1J_{\text{7-C,7-F}}$ 242.2 Hz), 145.32 (C-9a), 157.77 (C-8, $^1J_{\text{8-C,8-F}}$ 257.6 Hz), 167.33 (C-16), 172.29 (C-13), 173.46 (C-11), 186.55 (C-5). ^{19}F NMR, δ: 125.11 (ddd, 7-F, $^3J_{\text{7-F,8-F}}$ 22.0 Hz, $^3J_{\text{7-F,6-H}}$ 12.7 Hz, $^4J_{\text{7-F,9-H}}$ 9.8 Hz), 151.70 (ddd, 8-F, $^3J_{\text{8-F,7-F}}$ 22.0 Hz, $^3J_{\text{8-F,9-H}}$ 9.8 Hz, $^4J_{\text{8-F,6-H}}$ 5.9 Hz). MS, *m*/*z*: 439 (10%, M^+), 366 (100), 339 (25), 320 (20), 267 (40).



Scheme 2 *Reagents and conditions*: i, DMF, NaH, room temperature, 24 h; ii, H_2O, pH 7 (6% HCl).

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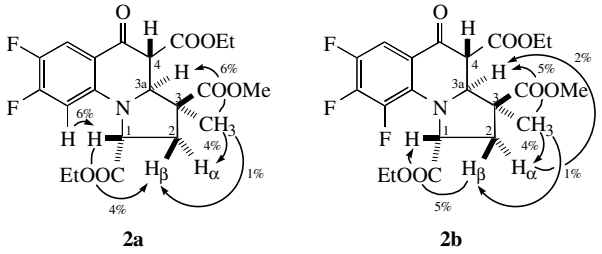
Compounds **2b**,**c** were obtained analogously.

2b (major isomer): yield 0.145 g (32%), mp 106–107 °C. ^{1}H NMR, δ: 1.23 (t, 3H, Me, ^3J 7.1 Hz), 1.32 (t, 3H, Me, ^3J 7.1 Hz), 1.32 (s, 3H, Me), 1.80 (dd, 1H, 2-H$_\alpha$, $^2J_{2\text{-H}_\alpha,2\text{-H}_\beta}$ 13.4 Hz, $^3J_{2\text{-H}_\alpha,1\text{-H}}$ 6.3 Hz), 3.11 (dd, 1H, 2-H$_\beta$, $^2J_{2\text{-H}_\beta,2\text{-H}_\alpha}$ 13.4 Hz, $^3J_{2\text{-H}_\beta,1\text{-H}}$ 9.5 Hz), 3.55 (d, 1H, 4-H, $^3J_{4\text{-H},3a\text{-H}}$ 14.5 Hz), 3.71 (s, 3H, COOMe), 4.18 (q, 2H, OCH$_2$, ^3J 7.1 Hz), 4.25 (d, 1H, 3a-H, $^3J_{3a\text{-H},4\text{-H}}$ 14.5 Hz), 4.29 (q, 2H, OCH$_2$, ^3J 7.1 Hz), 4.95 (dd, 1H, 1-H, $^3J_{1\text{-H},2\text{-H}_\alpha}$ 6.3 Hz, $^3J_{1\text{-H},2\text{-H}_\beta}$ 9.5 Hz), 7.46 (ddd, 1H, 6-H, $^3J_{6\text{-H},7\text{-F}}$ 9.9 Hz, $^4J_{6\text{-H},8\text{-F}}$ 8.1 Hz, $^5J_{6\text{-H},9\text{-F}}$ 2.1 Hz). ^{19}F NMR, δ: 148.33 (dd, 7-F, $^3J_{7\text{-F},8\text{-F}}$ 22.0 Hz, $^3J_{7\text{-F},6\text{-H}}$ 9.8 Hz), 149.35 (ddd, 8-F, $^3J_{8\text{-F},7\text{-F}}$ 22.0 Hz, $^3J_{8\text{-F},9\text{-F}}$ 17.1 Hz, $^4J_{8\text{-F},6\text{-H}}$ 8.3 Hz), 151.60 (ddd, 9-F, $^3J_{9\text{-F},8\text{-F}}$ 17.1 Hz, $^4J_{9\text{-F},7\text{-F}}$ 6.8 Hz, $^5J_{9\text{-F},6\text{-H}}$ 2.4 Hz). MS, *m*/*z*: 457 (M$^+$, 10%), 384 (100), 338 (15), 306 (20), 285 (25), 252 (25), 238 (30).

For **2c** (major isomer): yield 0.155 g (33%), mp 104–105 °C. ^{1}H NMR, δ: 1.27 (t, 3H, Me, ^3J 7.1 Hz), 1.35 (t, 3H, Me, ^3J 7.1 Hz), 1.35 (s, 3H, Me), 1.81 (dd, 1H, 2-H$_\alpha$, $^2J_{2\text{-H}_\alpha,2\text{-H}_\beta}$ 13.4 Hz, $^3J_{2\text{-H}_\alpha,1\text{-H}}$ 6.7 Hz), 3.11 (dd, 1H, 2-H$_\beta$, $^2J_{2\text{-H}_\beta,2\text{-H}_\alpha}$ 13.4 Hz, $^3J_{2\text{-H}_\beta,1\text{-H}}$ 9.2 Hz), 3.61 (d, 1H, 4-H, $^3J_{4\text{-H},3a\text{-H}}$ 14.0 Hz), 3.74 (s, 3H, OMe), 4.26 (q, 2H, OCH$_2$, ^3J 7.1 Hz), 4.28 (q, 1H, 3a-H, $^3J_{3a\text{-H},4\text{-H}}$ 13.7 Hz), 4.38 (q, 2H, OCH$_2$, ^3J 7.1 Hz), 5.01 (dd, 1H, 1-H, $^3J_{1\text{-H},2\text{-H}_\alpha}$ 6.7 Hz, $^3J_{1\text{-H},2\text{-H}_\beta}$ 9.5 Hz). ^{19}F NMR, δ: 141.86 (m, 1F), 147.26 (m, 1F), 158.56 (m, 1F), 172.59 (m, 1F). MS, *m*/*z*: 475 (M$^+$, 10%), 402 (100), 388 (18), 374 (15), 296 (15), 270 (18), 256 (28).



Scheme 3 Homonuclear ^{1}H–^{1}H Overhauser effects for compounds **2a** and **2b**.

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