

# Pyrido[2,3-*b*]- and pyrimido[4,5-*b*]quinoxalines: the first fluorine-containing derivatives

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Fluorinated derivatives of pyrido[2,3-*b*]- and pyrimido[4,5-*b*]quinoxalines **5–8** have been prepared through the condensation of 2-amino-3-cyano- and 2-amino-3-aminocarbonyl-substituted 6-fluoro-7-*R*-quinoxalines **1–4** with dimethyl acetylenedicarboxylate and triethyl orthoformate, respectively.

Quinoxaline 1,4-dioxides and their condensed analogues are biologically active compounds.<sup>1</sup> In particular, 2,3-di(hydroxymethyl)- and 2,3-di(acetoxymethyl)quinoxaline 1,4-dioxides are effective antibacterials.<sup>2</sup> We became interested in fluorinated derivatives of quinoxaline 1,4-dioxides<sup>3</sup> because the introduction of a fluorine atom into heterocyclic compounds can dramatically increase their biological potency, as exemplified by the development of the family of fluoroquinolones.<sup>4</sup> We have recently described novel derivatives of fluorinated furo[3,4-*b*] and pyrrolo[3,4-*b*]quinoxalines.<sup>5,6</sup> Now, we report the first synthesis of fluorinated pyrido[2,3-*b*]- and pyrimido[4,5-*b*]quinoxalines.

The published data<sup>2,7</sup> on the synthesis of pyrido[2,3-*b*]quinoxaline 5,10-dioxides are limited. Some derivatives of pyrido[2,3-*b*]quinoxalines proved to possess antibacterial and anti-

cancer activities.<sup>2,8,9</sup> Pyrimido[4,5-*b*]quinoxaline 5,10-dioxides are also little known, although these compounds proved to be antibacterials,<sup>10,11</sup> blood platelet anti-aggregating and antihypertensive agents.<sup>12</sup>

Aromatic *ortho*-aminonitriles are starting materials for the construction of fused pyridines through condensation reactions with dimethyl acetylenedicarboxylate (DMAD).<sup>13–15</sup> However, the annelation of a pyridine ring to quinoxalines by the condensation of *ortho*-aminonitriles with DMAD was not described previously. We have tried to apply this methodology to the synthesis of fluorinated pyrido[2,3-*b*]quinoxaline 5,10-dioxides on the basis of 2-amino-3-cyano-6-fluoro-7-*R*-substituted quinoxaline 1,4-dioxides **1a,b** used as the starting materials.<sup>3</sup> The reaction of **1a** with DMAD in DMSO or acetonitrile was found to proceed smoothly at room temperature in the presence of potassium carbonate to afford 2,3-bis(methoxycarbonyl)-7,8-difluoro-4-imino-1,4-dihydro-1*H*-pyrido[2,3-*b*]quinoxaline 5,10-dioxide **5a** in good yield (Scheme 1). The reaction takes only 30 min; prolongation of the reaction time up to 24 h has no effect. The reaction of **1b** with DMAD proceeds slower and requires 30 days at room temperature to be finished, however, at 60 °C, it goes much faster and takes 1 h. 2-Amino-3-cyano-6,7-difluoroquinoxaline **2** obtained from **1a** by reduction with sodium dithionite was found to react with DMAD in a similar way affording 2,3-bis(methoxycarbonyl)-7,8-difluoro-4-imino-1,4-dihydro-1*H*-pyrido[2,3-*b*]quinoxaline **6**. However, the reaction takes place only on heating in DMSO at 120 °C.

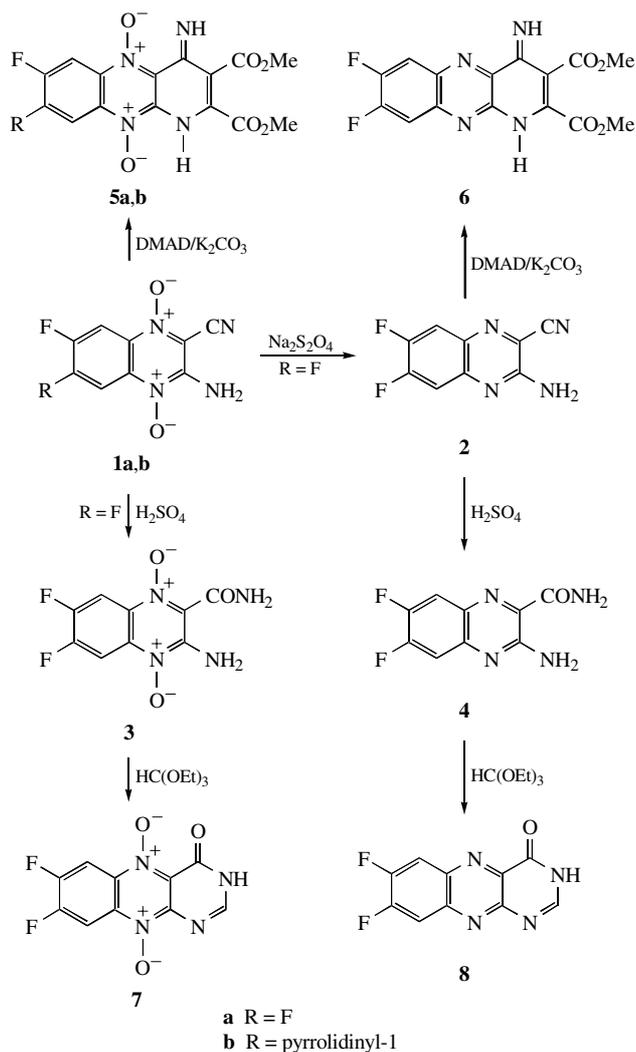
The fluorine derivatives of pyrimido[4,5-*b*]quinoxalines **7** and **8** were prepared in two steps: (i) by conversion of *ortho*-aminonitriles **1a** and **2** into corresponding carboxamides **3** and **4** on treatment with concentrated (98%) sulfuric acid (yields 87–92%) (Scheme 1), followed by (ii) cyclisation of *ortho*-aminocarboxamides **3** and **4** with triethyl orthoformate.

All compounds gave satisfactory elemental analyses and <sup>1</sup>H NMR, mass and IR spectra.<sup>†</sup>

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Scheme 1

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† 2-Amino-3-cyano-6,7-difluoroquinoxaline **2**. A solution of sodium dithionite (1.0 g, 6.0 mmol) in 15 ml of water was added dropwise to a suspension of compound **1a**<sup>3</sup> (0.48 g, 2.0 mmol) in 40 ml of ethanol. The reaction mixture was kept at 65–70 °C for 1.5 h with stirring and then cooled to 0–5 °C. The addition of cold water (60–70 ml) and stirring for 1 h at 5–10 °C gave a precipitate, which was filtered off and recrystallised from ethanol to give yellow crystals. Yield 0.25 g (61%), mp 201–202 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO) δ: 7.39 (br. s, 2H, NH<sub>2</sub>), 7.47 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 11.5 Hz, <sup>4</sup>J<sub>HF</sub> 8.0 Hz), 7.77 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 10.6 Hz, <sup>4</sup>J<sub>HF</sub> 8.0 Hz) (H-5 and H-8). IR (KBr, ν/cm<sup>-1</sup>): 3440–3240, 3040, 2240. MS, *m/z*: 206 (M<sup>+</sup>, 100).

2-Amino-3-aminocarbonyl-6,7-difluoroquinoxaline 1,4-dioxide **3**. Compound **1a** (0.5 g, 2.1 mmol) was added dropwise with stirring to 1.8 ml of concentrated sulfuric acid (*d* = 1.83), which was previously heated up to 55 °C. The reaction mixture was kept at 50–55 °C with stirring for 1 h and then at ambient temperature for 1 h, cooled to 0 °C and poured into ice. The reaction mixture was adjusted to pH 9 with aqueous ammonia and allowed to stand for 8–10 h in a refrigerator at 0–5 °C. The precipitate formed was filtered off and recrystallised from acetic acid to give orange crystals. Yield 0.47 g (87%), mp 265–266 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO) δ: 8.26 (br. s, 2H, NH<sub>2</sub>), 8.25 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 10.6 Hz, <sup>4</sup>J<sub>HF</sub> 7.6 Hz) and 8.42 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 10.6 Hz, <sup>4</sup>J<sub>HF</sub> 7.9 Hz), (H-5 and H-8), 8.56 (br. s, 1H, NH), 9.76 (br. s, 1H, NH). IR (KBr, ν/cm<sup>-1</sup>): 3400–3200, 3100–3000, 1670, 1380, 1340. MS *m/z*: 256 (M<sup>+</sup>, 100).

Compound **4** was obtained analogously to **3**. Yield 92%, mp 270–271 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO) δ: 7.54 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 12.1 Hz, <sup>4</sup>J<sub>HF</sub> 8.4 Hz) and 7.79 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 10.8 Hz, <sup>4</sup>J<sub>HF</sub> 8.6 Hz), (H-5 and H-8), 7.94 (br. s, 2H, NH<sub>2</sub>), 8.34 (br. s, 1H, NH), 9.46 (br. s, 1H, NH). IR (KBr, ν/cm<sup>-1</sup>): 3480–3320, 3320–3200, 1660. MS, *m/z*: 224 (M<sup>+</sup>, 100).

2,3-Bis(methoxycarbonyl)-7,8-difluoro-4-imino-1,4-dihydro-1H-pyrido[2,3-b]quinoxaline 5,10-dioxide **5a**. K<sub>2</sub>CO<sub>3</sub> (0.34 g, 2.5 mmol) was added to a solution of **1a** (0.24 g, 1.0 mmol) in 10 ml of DMSO or 35 ml of acetonitrile. Dimethyl acetylenedicarboxylate (DMAD) (0.21 g, 1.5 mmol) was added dropwise, and the reaction mixture was kept at ambient temperature for 0.5 h with stirring. The addition of cold water (70 ml) and stirring for 1 h at 5–10 °C gave a precipitate, which was filtered off and recrystallised from water–acetonitrile (1:1) to give red crystals. Yield 0.19 g (50%), mp 280–281 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO) δ: 3.86 (s, 3H, COOMe), 3.90 (s, 3H, COOMe), 8.54 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 10.2 Hz, <sup>4</sup>J<sub>HF</sub> 8.2 Hz) and 8.59 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 9.9 Hz, <sup>4</sup>J<sub>HF</sub> 8.0 Hz), (H-6 and H-9), 9.16 (br. s, 1H, =NH), 11.51 (br. s, 1H, NH). IR (KBr, ν/cm<sup>-1</sup>): 3370, 3230, 3070, 2950, 1730, 1680, 1340, 1300. MS, *m/z*: 380 (M<sup>+</sup>, 74).

2,3-Bis(methoxycarbonyl)-7-fluoro-4-imino-8-(pyrrolidin-1-yl)-1,4-dihydro-1H-pyrido[2,3-b]quinoxaline 5,10-dioxide **5b**. Potassium carbonate (0.18 g, 1.3 mmol) was added to a solution of compound **1b**<sup>3</sup> (0.15 g, 0.5 mmol) in 10 ml of DMSO. DMAD (0.11 g, 0.75 mmol) was added dropwise, and the reaction mixture was kept at 60 °C for 1 h with stirring and then cooled to 0–5 °C and allowed to stand at this temperature for 1 h. The precipitate was filtered off and recrystallised from ethanol to give dark red crystals. Yield 0.13 g (88%), mp 250–252 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO) δ: [2.27 (m, 4H), 3.44 (m, 4H), pyrrolidin-1-yl], 3.86 (s, 3H, COOMe), 3.90 (s, 3H, COOMe), 7.23 (d, 1H, H-9, <sup>4</sup>J<sub>HF</sub> 8.9 Hz), 8.12 (d, 1H, H-6, <sup>3</sup>J<sub>HF</sub> 14.4 Hz), 9.16 (br. s, 1H, =NH), 11.51 (br. s, 1H, NH). IR (KBr, ν/cm<sup>-1</sup>): 3330–3300, 2950–2860, 1740, 1700, 1350, 1310. MS, *m/z*: 431 (M<sup>+</sup>, 70).

2,3-Bis(methoxycarbonyl)-7,8-difluoro-4-imino-1,4-dihydro-1H-pyrido[2,3-b]quinoxaline **6**. K<sub>2</sub>CO<sub>3</sub> (0.14 g, 1.0 mmol) was added to a solution of compound **2** (0.1 g, 0.4 mmol) in 10 ml of DMSO. DMAD (0.085 g, 0.6 mmol) was added dropwise, and the reaction mixture was kept at 120 °C for 1 h with stirring and then cooled to 0–5 °C. The addition of cold water (50 ml) and stirring for 1 h at 5–10 °C gave a precipitate, which was filtered off and recrystallised from ethanol to give dark red crystals. Yield 0.12 g (71%), mp 239–240 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO) δ: 3.89 (s, 3H, COOMe), 3.91 (s, 3H, COOMe), 7.95 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 10.7 Hz, <sup>4</sup>J<sub>HF</sub> 8.7 Hz) and 8.25 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 11.2 Hz, <sup>4</sup>J<sub>HF</sub> 8.4 Hz), (H-6 and H-9), 8.60 (br. s, 1H, =NH), 8.82 (br. s, 1H, NH). IR (KBr, ν/cm<sup>-1</sup>): 3430–3240, 3050–2850, 1740, 1700. MS, *m/z*: 348 (M<sup>+</sup>, 78).

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7,8-Difluoropyrimido[4,5-b]quinoxaline-4(3H)-one 5,10-dioxide **7**. A mixture of compound **3** (0.2 g, 0.8 mmol) and triethyl orthoformate (10 ml) was refluxed for 20 h. The resulting dark orange solution was evaporated to dryness *in vacuo*. The solid was recrystallised from acetic acid to give yellow crystals. Yield 26%, mp > 300 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO) δ: 8.25 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 11.3 Hz, <sup>4</sup>J<sub>HF</sub> 8.2 Hz) and 8.40 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 10.7 Hz, <sup>4</sup>J<sub>HF</sub> 8.6 Hz), (H-6 and H-9), 8.43 (s, 1H, H-2), 12.74 (br. s, 1H, NH). IR (KBr, ν/cm<sup>-1</sup>): 3500–3300, 3050, 1700, 1380, 1300. MS, *m/z*: 266 (M<sup>+</sup>, 100).

7,8-Difluoropyrimido[4,5-b]quinoxaline-4(3H)-one **8**. A mixture of compound **4** (0.1 g, 0.45 mmol) and triethyl orthoformate (5 ml) was refluxed for 1.5 h. The resulting brown solution was cooled; the precipitate formed was filtered off and recrystallised from acetic acid to give yellow crystals. Yield 87%, mp > 300 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO) δ: 8.22 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 11.3 Hz, <sup>4</sup>J<sub>HF</sub> 8.6 Hz) and 8.38 (dd, 1H, <sup>3</sup>J<sub>HF</sub> 11.0 Hz, <sup>4</sup>J<sub>HF</sub> 8.5 Hz), (H-6 and H-9), 8.43 (s, 1H, H-2), 12.74 (br. s, 1H, NH). IR (KBr, ν/cm<sup>-1</sup>): 3050, 2900–2700, 1700. MS, *m/z*: 234 (M<sup>+</sup>, 100).