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

Valerii N. Charushin,* Svetlana K. Kotovskaya, Natalya M. Perova and Oleg N. Chupakhin

Department of Organic Chemistry, Urals State Technical University, 620002 Ekaterinburg, Russian Federation. Fax: +7 3422 74 0458; e-mail: charushin@htf.ustu.ru

10.1070/MC2001v011n02ABEH001333

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.

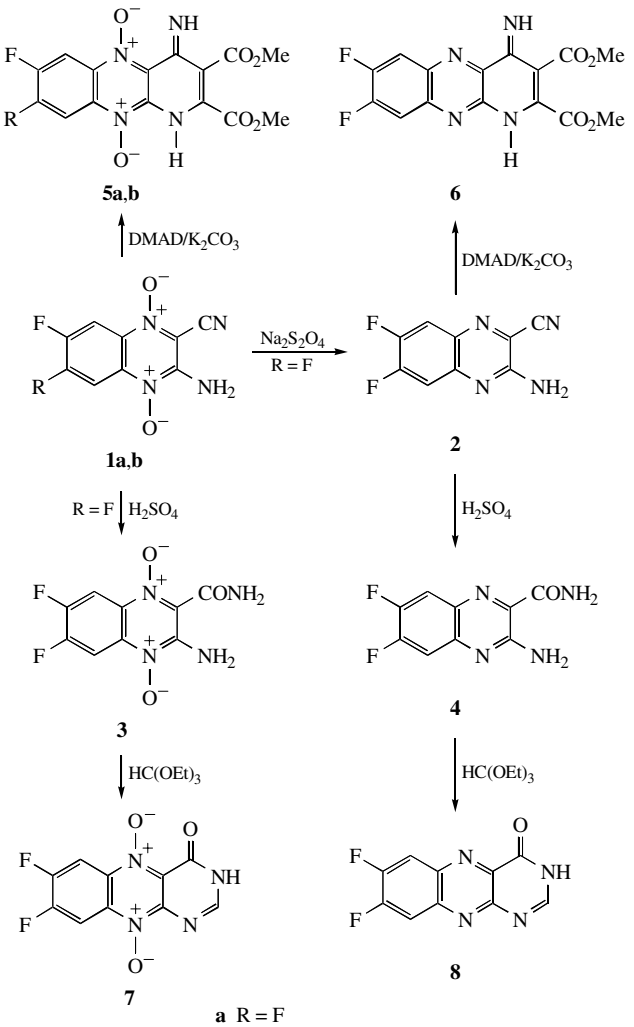
Quinoxaline 1,4-dioxides and their condensed analogues are biologically active compounds.[1] In particular, 2,3-di(hydroxymethyl)- and 2,3-di(acetoxymethyl)quinoxaline 1,4-dioxides are effective antibacterials.[2] We became interested in fluorinated derivatives of quinoxaline 1,4-dioxides[3] because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

The published data[2,7] 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 anticancer activities.[2,8,9] Pyrimido[4,5-*b*]quinoxaline 5,10-dioxides are also little known, although these compounds proved to be antibacterials,[10,11] blood platelet anti-aggregating and antihypertensive agents.[12]

Aromatic *ortho*-aminonitriles are starting materials for the construction of fused pyridines through condensation reactions with dimethyl acetylenedicarboxylate (DMAD).[13–15] 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.[3] 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 ^{1}H NMR, mass and IR spectra.†



Scheme 1

This work was supported by the US Civilian Research and Development Foundation (grant no. REC-005) and the Russian Foundation for Basic Research (grant no. 00-03-32785).

References

1 Y. Kurasava, A. Takada and H. S. Kim, *J. Heterocycl. Chem*., 1995, **32**, 1085.
2 G. W. H. Cheesman and R. F. Cookson, in *The Chemistry of Heterocyclic Compounds*, eds. A. Weisberger and E. C. Taylor, Wiley–Interscience, New York, 1979, vol. 35.
3 S. K. Kotovskaya, V. N. Charushin, O. N. Chupakhin and E. O. Kozhevnikova, *Zh. Org. Khim*., 1998, **34**, 399 (*Russ. J. Org. Chem*., 1998, **34**, 369).
4 D. Bouzard, in *Antibiotics and Antiviral Compounds*, eds. K. Krohn, H. A. Rirst and H. Maag, VCH, Weinheim, 1993.
5 O. N. Chupakhin, S. K. Kotovskaya, N. M. Perova, Z. M. Baskakova and V. N. Charushin, *Khim. Geterotsikl. Soedin*., 1999, 520 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1999, **35**, 459].
6 S. K. Kotovskaya, N. M. Perova, V. N. Charushin and O. N. Chupakhin, *Mendeleev Commun*., 1999, 76.
7 M. J. Abu El-Haj, B. W. Doming, J. D. Johnston, M. J. Haddadin and C. H. Jssidorides, *J. Org. Chem*., 1972, **37**, 589.

8 M. Pesson, P. De Lajudie, M. Antoine, S. Cnabassin and P. Gurard, *C. R. Acad. Sci., Ser. C*, 1976, **282**, 861 (*Chem. Abstr*., 1976, **85**, 63035).
9 W. Parri, *Giorn, Ital. Chemioterap*., 1956, **3**, 588 (*Chem. Abstr*., 1958, **52**, 11289).
10 F. Seng and K. Ley, *German Patent* 2.034.476, 1971 (*Chem. Abstr*., 1972, **76**, 153787f).
11 F. Seng and K. Ley, *German Patent* 2.122.571, 1973 (*Chem. Abstr*., 1973, **78**, 43522z).
12 A. Monge, J. A. Palop and I. Urbasos, *J. Heterocycl. Chem*., 1989, **26**, 1623.
13 E. C. Taylor and A. McKillop, in *Advances in Organic Chemistry, The Chemistry of Cyclic Enaminonitrile and* o-*Aminonitrile*, ed. E. C. Taylor, Interscience, New York, 1970, vol. 7.
14 J. M. Robinson, L. W. Brent, C. Chau, K. A. Floyd, S. L. Gillham, T. L. McMaham, D. J. Magda, T. J. Motycka, M. J. Pack, F. L. Roberts, L. A. Seally, S. L. Simpson, R. R. Smith and K. N. Zaiesny, *J. Org. Chem*., 1992, **57**, 7352.
15 Y. Tominaga and N. Yoshioka, *Heterocycles*, 1996, **42**, 53.

† *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**[3] (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. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.39 (br. s, 2H, NH_2), 7.47 (dd, 1H, $^3J_{HF}$ 11.5 Hz, $^4J_{HF}$ 8.0 Hz), 7.77 (dd, 1H, $^3J_{HF}$ 10.6 Hz, $^4J_{HF}$ 8.0 Hz) (H-5 and H-8). IR (KBr, ν/cm^{-1}): 3440–3240, 3040, 2240. MS, *m*/*z*: 206 (M$^+$, 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 refregerator 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. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.26 (br. s, 2H, NH_2), 8.25 (dd, 1H, $^3J_{HF}$ 10.6 Hz, $^4J_{HF}$ 7.6 Hz) and 8.42 (dd, 1H, $^3J_{HF}$ 10.6 Hz, $^4J_{HF}$ 7.9 Hz), (H-5 and H-8), 8.56 (br. s, 1H, NH), 9.76 (br. s, 1H, NH). IR (KBr, ν/cm^{-1}): 3400–3200, 3100–3000, 1670, 1380, 1340. MS *m*/*z*: 256 (M$^+$, 100).

Compound **4** was obtained analogously to **3**. Yield 92%, mp 270–271 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.54 (dd, 1H, $^3J_{HF}$ 12.1 Hz, $^4J_{HF}$ 8.4 Hz) and 7.79 (dd, 1H, $^3J_{HF}$ 10.8 Hz, $^4J_{HF}$ 8.6 Hz), (H-5 and H-8), 7.94 (br. s, 2H, NH_2), 8.34 (br. s, 1H, NH), 9.46 (br. s, 1H, NH). IR (KBr, ν/cm^{-1}): 3480–3320, 3320–3200, 1660. MS, *m*/*z*: 224 (M$^+$, 100).

*2,3-Bis(methoxycarbonyl)-7,8-difluoro-4-imino-1,4-dihydro-1*H*-pyrido-[2,3-*b*]quinoxaline 5,10-dioxide* **5a**. K_2CO_3 (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. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.86 (s, 3H, COOMe), 3.90 (s, 3H, COOMe), 8.54 (dd, 1H, $^3J_{HF}$ 10.2 Hz, $^4J_{HF}$ 8.2 Hz) and 8.59 (dd, 1H, $^3J_{HF}$ 9.9 Hz, $^4J_{HF}$ 8.0 Hz), (H-6 and H-9), 9.16 (br. s, 1H, =NH), 11.51 (br. s, 1H, NH). IR (KBr, ν/cm^{-1}): 3370, 3230, 3070, 2950, 1730, 1680, 1340, 1300. MS, *m*/*z*: 380 (M$^+$, 74).

*2,3-Bis(methoxycarbonyl)-7-fluoro-4-imino-8-(pyrrolidin-1-yl)-1,4-dihydro-1*H*-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**[3] (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. ^{1}H NMR ([$^2H_6$]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, $^4J_{HF}$ 8.9 Hz), 8.12 (d, 1H, H-6, $^3J_{HF}$ 14.4 Hz), 9.16 (br. s, 1H, =NH), 11.51 (br. s, 1H, NH). IR (KBr, ν/cm^{-1}): 3330–3300, 2950–2860, 1740, 1700, 1350, 1310. MS, *m*/*z*: 431 (M$^+$, 70).

*2,3-Bis(methoxycarbonyl)-7,8-difluoro-4-imino-1,4-dihydro-1*H*-pyrido-[2,3-*b*]quinoxaline* **6**. K_2CO_3 (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. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.89 (s, 3H, COOMe), 3.91 (s, 3H, COOMe), 7.95 (dd, 1H, $^3J_{HF}$ 10.7 Hz, $^4J_{HF}$ 8.7 Hz) and 8.25 (dd, 1H, $^3J_{HF}$ 11.2 Hz, $^4J_{HF}$ 8.4 Hz), (H-6 and H-9), 8.60 (br. s, 1H, =NH), 8.82 (br. s, 1H, NH). IR (KBr, ν/cm^{-1}): 3430–3240, 3050–2850, 1740, 1700. MS, *m*/*z*: 348 (M$^+$, 78).

Received: 26th May 2000; Com. 00/1659

*7,8-Difluoropyrimido[4,5-*b*]quinoxaline-4(3*H*)-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. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.25 (dd, 1H, $^3J_{HF}$ 11.3 Hz, $^4J_{HF}$ 8.2 Hz) and 8.40 (dd, 1H, $^3J_{HF}$ 10.7 Hz, $^4J_{HF}$ 8.6 Hz), (H-6 and H-9), 8.43 (s, 1H, H-2), 12.74 (br. s, 1H, NH). IR (KBr, ν/cm^{-1}): 3500–3300, 3050, 1700, 1380, 1300. MS, *m*/*z*: 266 (M$^+$, 100).

*7,8-Difluoropyrimido[4,5-*b*]quinoxaline-4(3*H*)-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. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.22 (dd, 1H, $^3J_{HF}$ 11.3 Hz, $^4J_{HF}$ 8.6 Hz) and 8.38 (dd, 1H, $^3J_{HF}$ 11.0 Hz, $^4J_{HF}$ 8.5 Hz), (H-6 and H-9), 8.43 (s, 1H, H-2), 12.74 (br. s, 1H, NH). IR (KBr, ν/cm^{-1}): 3050, 2900–2700, 1700. MS, *m*/*z*: 234 (M$^+$, 100).