One-step route to fluorinated furo[2,3-*b*]quinoxalines

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The reaction of 6,7-difluoro-1-ethylquinoxalinium salts with 2,4-pentanedione, ethyl and bornyl acetoacetates and other β-keto esters results in the formation of 6,7-difluoro-3a,4,9,9a-tetrahydrofuro[2,3-*b*]quinoxalines. In addition, asymmetric 6-fluoro-7-morpholino and 6-fluoro-7-thiomorpholino substituted 1-ethylquinoxalinium salts react with alkyl acetoacetates in a regio- and stereoselective manner, thus giving exclusively the corresponding alkyl 2-methyl-6-fluoro-7-substituted 3a,4,9,9a-tetrahydrofuro[2,3-*b*]quinoxalin-3-carboxylates.

A common way to condensed azines is based on the use of displacement reactions in which electron-deficient azines bearing two halogen atoms or other leaving groups in the *ortho*-position to each other are allowed to react with bifunctional nucleophilic reagents (for a review see ref. 1). For instance, 2,3,5,6-tetrachloropyrazine has been found to react with ethyl acetoacetate to give ethyl 2-methyl-5,6-dichlorofuro[2,3-*b*]-pyrazine-3-carboxylate (Scheme 1).[2]

We have developed a new methodology for the synthesis of a variety of condensed heterocyclic systems based on diaddition-type cyclizations of bifunctional nucleophiles with quaternary 1-alkyl-1,4-diazinium salts, their aza and benzo analogues bearing no nucleofugal groups (Scheme 2).[3–8]

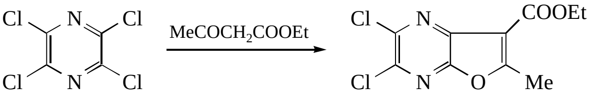
In this paper we describe the first examples of the *ortho*-cyclization reaction in the series of fluorinated 1-ethylquinoxalinium salts **1** and **2a**,**b**.

6,7-Difluoroquinoxaline and 6,7-difluoro-1-ethylquinoxalinium tetrafluoroborate **1** became available very recently.[9] It has also been shown that both fluorine atoms in these molecules can be replaced with nucleophiles.[9] In particular, substitution of the fluorine atom at C(7) by amines in **1** occurs very easily at 10–15 °C, yielding the corresponding 6-fluoro-7-substituted 1-ethylquinoxalinium tetrafluoroborates **2a**,**b**.[7] Taking into account the good leaving ability of both fluorine atoms in **1**, it might be expected that nucleophilic mono- or disubstitution reactions would have to take place in the reaction of **1** with β-dicarbonyl compounds. On the other hand, the 1,4-diazinium salts are capable of reacting with bifunctional nucleophiles to give condensed tetrahydropyrazines, due to the diaddition reaction of enolates on C(2) and C(3) of the pyrazine ring.[3,4]

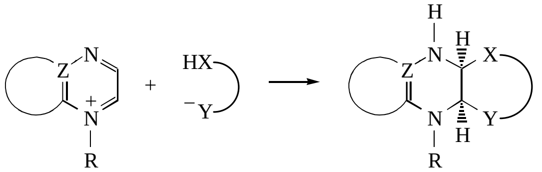
We have found that in the reaction of 6,7-difluoro-1-ethylquinoxalinium tetrafluoroborate **1** with 2,4-pentanedione and alkyl acetoacetates, including ethyl, bornyl, isobornyl or structurally more complicated esters, the diaddition of these enolates at C(2) and C(3) of the pyrazine ring proceeds much faster than the displacement of fluorine atoms in the benzene ring, thus resulting in fluorinated derivatives of 3a,4,9,9a-tetrahydrofuro-[2,3-*b*]quinoxalines **3a**–**e** in high yields (Scheme 3).[†,‡]

The cyclization reaction demonstrates high regio- and stereo-selectivity. Even in those cases when asymmetric 6-fluoro-7-morpholino **2a** and 6-fluoro-7-thiomorpholino **2b** substituted quinoxalinium salts **2a**,**b** reacted with alkyl acetoacetates, no regio- or stereo-isomeric products, apart from furo[2,3-*b*]-quinoxalines **4a**–**d**, were obtained.

Evidence for the structure of compounds **3a**–**e** and **4a**–**d** is provided by their ^{1}H[‡] and ^{19}F NMR spectra. The H(3a) signal can easily be assigned in the ^{1}H NMR spectra of **3a**–**e** and **4a**–**d** since it is coupled to the N–H proton. Another specific feature is a long-range coupling constant between H(3a) and the C(2)–*Me* protons. The fact that H(3a) resonates at a higher field (4.7–5.0 ppm) than H(9a) (5.8–6.0 ppm) suggests that the H(9a) resonance is affected by the neighbouring electronegative oxygen atom. Also, X-ray crystallographic analysis performed for the acyl derivative of **3e**, 1-(isopropyloxycarbonyl)ethyl 2-methyl-4-acetyl-9-ethyl-6,7-difluoro-3a,4,9,9a-tetrahydrofuro-[2,3-*b*]quinoxalin-3-carboxylate **5**,[§] gave unequivocal evidence for the structure. This revealed that the tetrahydropyrazine ring



Scheme 1



R = alkyl; Z = N, CR, benzo; X and Y are N-, O- or C-nucleophilic centres

Scheme 2

[†] A typical experimental procedure for the synthesis of fluorinated furo[2,3-*b*]quinoxalines **3a**–**e** and **4a**–**d**.

Isobornyl 2-methyl-9-ethyl-6,7-difluoro-3a,4,9,9a-tetrahydrofuro[2,3-b]-quinoxalin-3-carboxylate **3d**. Diethylamine (0.36 ml, 3.6 mmol) was added dropwise to a mixture of 6,7-difluoro-1-ethylquinoxalinium tetrafluoroborate **1** (1 g, 3.5 mmol) and isobornyl acetoacetate (1 ml, 3.7 mmol) in 4 ml of ethanol at ambient temperature with stirring until dissolving of the reactants was complete. In a few minutes, when colourless crystals of compound **3d** started to appear, the reaction mixture was put into an ice-bath for 2–3 h and the crystalline product was filtered off, washed with cool ethanol and dried in air. Recrystallization from hexane gave colourless crystals of **3d** with mp 125 °C. Yield 1.1 g (72%).

Compounds **3a**–**c**,**e** and **4a**–**d** were obtained similarly.

1-(Isopropyloxycarbonyl)ethyl 2-methyl-4-acetyl-9-ethyl-6,7-difluoro-3a,4,9,9a-tetrahydrofuro[2,3-b]quinoxalin-3-carboxylate **5**. Acetic anhydride (5 ml, 50 mmol) was added to 1-(isopropyloxycarbonyl)ethyl 2-methyl-9-ethyl-6,7-difluoro-3a,4,9,9a-tetrahydrofuro[2,3-*b*]quinoxalin-3-carboxylate **3e** (0.5 g, 1.2 mmol). The reaction mixture was refluxed for 5 min and left to stand at room temperature for 24 h. The crystalline product obtained was filtered off and recrystallized from aqueous 80% ethanol. Yield 0.4 g (72%), mp 153 °C.

[‡] **3a**: yield 75%, mp 121–122 °C (decomp.); ^{1}H NMR (CDCl$_3$) δ: 4.98 [H(3a)], 5.83 [H(9a)], $^3J_{\mathrm{H(3a)–H(9a)}}$ 7.9 Hz.

3b: yield 78%, mp 129–130 °C (decomp.); ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 4.65 [H(3a)], 5.85 [H(9a)], $^3J_{\mathrm{H(3a)–H(9a)}}$ 8.2 Hz.

3c: yield 75%, mp 133–134 °C (decomp.); ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 4.65 [H(3a)], 6.05 [H(9a)], $^3J_{\mathrm{H(3a)–H(9a)}}$ 8.0 Hz.

3d: yield 72%, mp 125 °C (decomp.); ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 4.90 [H(3a)], 5.87 [H(9a)], $^3J_{\mathrm{H(3a)–H(9a)}}$ 7.9 Hz.

3e: yield 73%, mp 120 °C (decomp.); ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 4.95 [H(3a)], 5.91 [H(9a)], $^3J_{\mathrm{H(3a)–H(9a)}}$ 9.0 Hz.

4a: yield 84%, mp 125–126 °C (decomp.); ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 4.70 [H(3a)], 5.98 [H(9a)], $^3J_{\mathrm{H(3a)–H(9a)}}$ 8.2 Hz.

4b: yield 83%, mp 135 °C (decomp.); ^{1}H NMR (CDCl$_3$) δ: 4.85 [H(3a)], 5.85 [H(9a)], $^3J_{\mathrm{H(3a)–H(9a)}}$ 8.7 Hz.

4c: yield 80%, mp 134–135 °C (decomp.); ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 4.68 [H(3a)], 5.96 [H(9a)], $^3J_{\mathrm{H(3a)–H(9a)}}$ 8.0 Hz.

4d: yield 90%, mp 145–146 °C (decomp.); ^{1}H NMR (CDCl$_3$) δ: 4.85 [H(3a)], 5.85 [H(9a)], $^3J_{\mathrm{H(3a)–H(9a)}}$ 8.7 Hz.

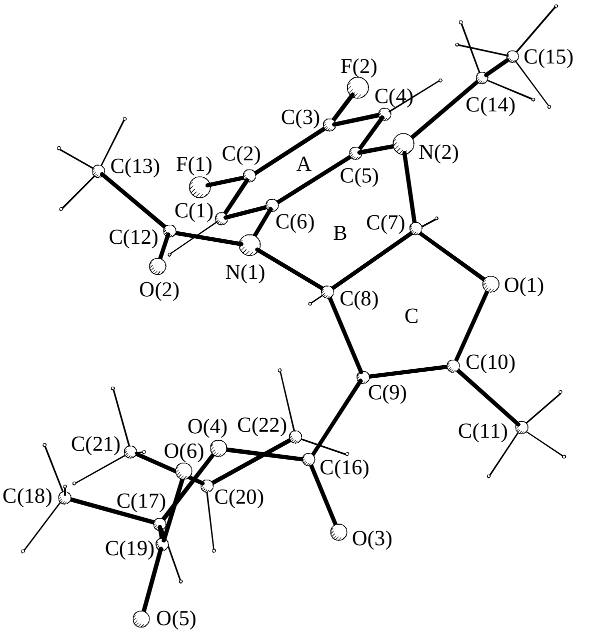
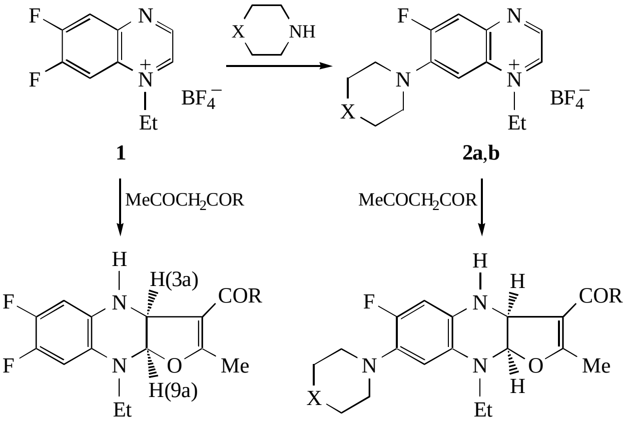


Figure 1 Molecular structure and numbering of atoms for compound **5**. Enumeration of atoms does not correspond to IUPAC nomenclature. Selected bond lengths/Å and bond angles/° for compound **5**: F(1)–C(2) 1.356(3), F(2)–C(3) 1.351(2), N(1)–C(12) 1.373(3), N(1)–C(6) 1.419(2), N(1)–C(8) 1.470(2), N(2)–C(5) 1.407(3), N(2)–C(7) 1.428(3), N(2)–C(14) 1.474(3), O(1)–C(10) 1.356(3), O(1)–C(7) 1.482(2), O(2)–C(12) 1.216(2), O(3)–C(16) 1.213(2), O(4)–C(16) 1.354(2), O(4)–C(17) 1.444(3), O(5)–C(19) 1.198(3), O(6)–C(19) 1.328(3), O(6)–C(20) 1.472(3), C(1)–C(2) 1.373(3), C(1)–C(6) 1.379(3), C(2)–C(3) 1.362(3), C(3)–C(4) 1.379(3), C(4)–C(5) 1.387(3), C(5)–C(6) 1.405(3), C(7)–C(8) 1.549(3), C(8)–C(9) 1.508(3), C(9)–C(10) 1.342(3), C(9)–C(16) 1.447(3), C(10)–C(11) 1.482(3), C(12)–C(13) 1.506(3), C(14)–C(15) 1.507(4), C(17)–C(19) 1.514(3), C(17)–C(18) 1.515(4), C(20)–C(21) 1.483(5), C(20)–C(22) 1.491(4); C(12)–N(1)–C(6) 125.6(2), C(12)–N(1)–C(8) 119.9(2), C(6)–N(1)–C(8) 113.7(2), C(5)–N(2)–C(7) 114.3(2), C(5)–N(2)–C(14) 117.3(2), C(7)–N(2)–C(14) 116.0(2), C(10)–O(1)–C(7) 108.7(2), C(16)–O(4)–C(17) 115.0(2), C(19)–O(6)–C(20) 118.4(2), C(2)–C(1)–C(6) 118.7(2), F(1)–C(2)–C(3) 119.5(2), F(1)–C(2)–C(1) 119.7(2), C(3)–C(2)–C(1) 120.8(2), F(2)–C(3)–C(2) 119.2(2), F(2)–C(3)–C(4) 119.2(2), C(2)–C(3)–C(4) 121.6(2), C(3)–C(4)–C(5) 118.7(2), C(4)–C(5)–C(6) 119.1(2), C(4)–C(5)–N(2) 124.6(2), C(6)–C(5)–N(2) 116.2(2), C(1)–C(6)–C(5) 120.9(2), C(1)–C(6)–N(1) 123.5(2), C(5)–C(6)–N(1) 115.5(2), N(2)–C(7)–O(1) 110.0(2), N(2)–C(7)–C(8) 113.5(2), O(1)–C(7)–C(8) 105.3(2), N(1)–C(8)–C(9) 114.9(2), N(1)–C(8)–C(7) 110.6(2), C(9)–C(8)–C(7) 102.3(2), C(10)–C(9)–C(16) 124.5(2), C(10)–C(9)–C(8) 109.8(2), C(16)–C(9)–C(8) 125.7(2), C(9)–C(10)–O(1) 113.9(2), C(9)–C(10)–C(11) 131.9(2), O(1)–C(10)–C(11) 114.1(2), O(2)–C(12)–N(1) 121.1(2), O(2)–C(12)–C(13) 121.3(2), N(1)–C(12)–C(13) 117.6(2), N(2)–C(14)–C(15) 112.1(2), O(3)–C(16)–O(4) 121.8(2), O(3)–C(16)–C(9) 126.7(2), O(4)–C(16)–C(9) 111.5(2), O(4)–C(17)–C(19) 111.5(2), O(4)–C(17)–C(18) 106.4(2), C(19)–C(17)–C(18) 111.1(2), O(5)–C(19)–O(6) 125.1(2), O(5)–C(19)–C(17) 122.3(2), O(6)–C(19)–C(17) 112.6(2), O(6)–C(20)–C(21) 108.7(3), O(6)–C(20)–C(22) 105.9(2), C(21)–C(20)–C(22) 113.4(3).



1

2a,**b**

3a–e

4a–d

a R = Me
b R = OEt
c R = *O*-bornyl
d R = *O*-isobornyl
e R = OCHMeCOOCHMe$_2$

a R = OEt, X = O
b R = *O*-isobornyl, X = O
c R = OEt, X = S
d R = *O*-isobornyl, X = S

Scheme 3

in **5** exists in a boat conformation with two nitrogen atoms deviating from the average plane of the other four carbons by –0.54 and –0.50 Å, respectively. The dihedral angle between the benzene ring A and the average plane of the four carbons of the tetrahydropyrazine ring B is 156.1°, while the dihedral angle between the rings B and C of the heterocyclic fragment is 98.7° (Figure 1). It is also worth noting that the ring junction hydrogen atoms are in a *cis*-orientation, thus forming a torsion angle H–C(7)–C(8)–H of 3.1°.

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Received: Moscow, 27th April 1998
Cambridge, 4th June 1998; Com. 8/03518K

[§] X-ray crystallographic data for **5** were obtained at 20 °C on a ‘CAD-4’ diffractometer (MoKα radiation, graphite monochromator, ω-scan, $2\theta_{max} = 60°$). The structure was solved by a direct method and refined by a full-matrix least-squares method in an anisotropic approximation (isotropic for hydrogen atoms) using programs SHELXL-93 to $R = 0.0386$ for 3040 independent reflections with $F^2 > 3\sigma(I)$; $F(000) = 476$, largest diff. peak and hole are 0.172 and –0.175 Å^{-3}, respectively. Empirical formula $C_{22}H_{26}F_2N_2O_6$, triclinic crystals, space group $P1$, $a = 8.755(1)$ Å, $b = 10.382(2)$ Å, $c = 12.418(2)$ Å, $\alpha = 80.61°$, $\beta = 87.96°$, $\gamma = 78.96°$, $V = 1093.0(3)$ Å^3, $d_{calc} = 1.375$ g cm^{-3}, $Z = 2$. Bond angles, bond lengths and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see ‘Notice to Authors’, *Mendeleev Commun.*, 1998, Issue 1. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/26.