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New way of the reaction of 1-amino-6,7-difluoro-4-oxoquinolyl-3-ethylcarboxylate with acetoacetone

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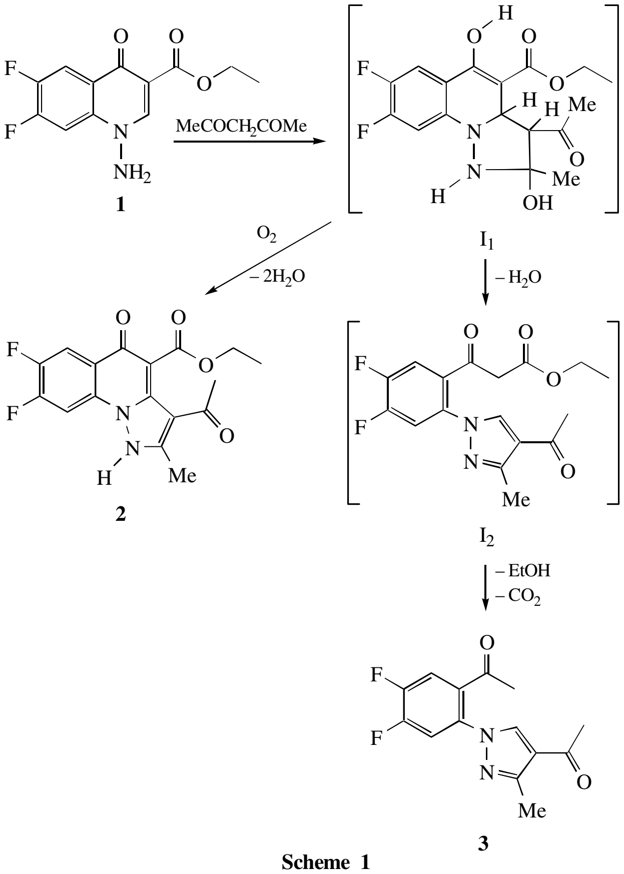
The reaction of 1-amino-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-ethylcarboxylate 1 with acetoacetone in acetic acid without air yielded 1-(2-acetyl-4,5-difluorophenyl)-3-methyl-4-acetylpyrazole 3.

New synthetic antibiotics named fluoroquinolones are widely used in medicine and veterinary medicine as highly effective antibacterial drugs.[1–5] Formerly,[6] we reported a synthetic way to new tricyclic fluoroquinolones, pyrazolo[1,5-*a*]quinolones, by the cyclization of 7-substituted 1-amino-6-fluoro-1,4-dihydro-4-oxoquinoline-3-ethylcarboxylates with β-diketones (Scheme 1).



Scheme 1

The formation of pyrazoloquinolones **2** by oxidation of adduct intermediates was confirmed by an acceleration of the reaction and an increase in yield when air was bubbled through the reaction mixture.

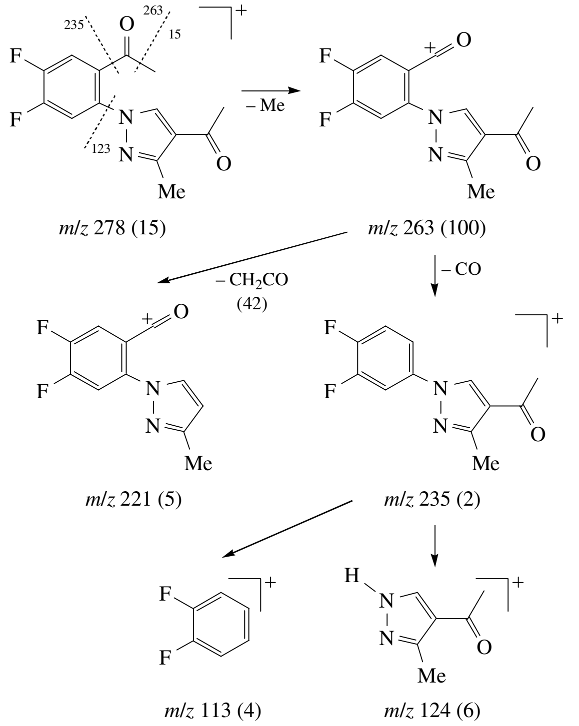
In this work, we found a new way of the reaction of 1-amino-4-oxoquinoline-3-ethylcarboxylate **1** with acetoacetone. On heating **1** with acetoacetone in acetic acid without air, 1-(2-acetyl-4,5-difluorophenyl)-3-methyl-4-acetylpyrazole **3** was obtained.

In the ^{1}H NMR spectra of **3** in [^{2}H$_6$]DMSO,† proton signals of three Me groups are present: the 3-Me group of the pyrazole fragment at 2.14 ppm and two acetyl groups at 2.33 and 2.40 ppm. The multiplets of two aromatic protons are at 7.15–8.00 ppm, and the singlet of pyrazole CH is at 8.7 ppm.

The electron impact mass spectrum (EI MS) of **3** shows a weak molecular ion peak at *m/z* 278 (15%) corresponding to the molecular formula $C_{14}H_{12}F_2N_2O_2$. The molecular formula $C_{14}H_{12}F_2N_2O_2$ of product **3** was confirmed by high resolution mass spectrometry ($C_{14}H_{12}F_2N_2O_2$, experimental 278.08668, calculated 278.08668, Δ 3.8). The most intense peak in the EI mass spectrum has *m/z* 263 ([M – Me]$^+$). The fragmentation of $M^{+\cdot}$ corresponds to the proposed structure of **3** (Scheme 2).

The structure of **3** was unequivocally established by X-ray analysis‡ (Figure 1). The phenyl and pyrazole rings of compound **3** are non-coplanar with a dihedral angle equal to 30±3°.

In conclusion, the new reaction of *N*-aminoquinolone **1** with acetoacetone confirms the mechanism[6] of formation of pyrazolo-[1,5-*a*]quinolones with the participation of O_2.[6] This reaction



Scheme 2

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† ^{1}H NMR spectra were recorded on a Bruker DPX 200 spectrometer. Chemical shifts were measured with DMSO as an internal standard. Electron impact mass spectra were recorded on a Finnigan MAT 8200 mass spectrometer with a 70 eV electron energy.

1-(2-Acetyl-4,5-difluorophenyl)-3-methyl-4-acetylpyrazole **3**. Argon was bubbled through a solution of 2.0 g (7.46 mmol) of 1-amino-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-ethylcarboxylate **1** and 7.5 ml acetylacetone in 30 ml of acetic acid (> 99.9%) for 1–2 min. The reaction mixture was refluxed for 3.5–4 h away from air. Then, it was cooled, diluted with water (1:1) and extracted with chloroform. The extract was evaporated *in vacuo*. Solid product **3** was recrystallised from heptane. Yield, 1.2 g (58%), mp 110–111 °C.

^{1}H NMR ([^{2}H$_6$]DMSO) δ: 2.15 (s, 3H, Me), 2.33 (s, 3H, COMe), 2.40 (s, 3H, COMe), 7.15–8.00 (m, 2H, H-3 arom. + H-6 arom.), 8.97 (s, 1H, pyrazole CH).

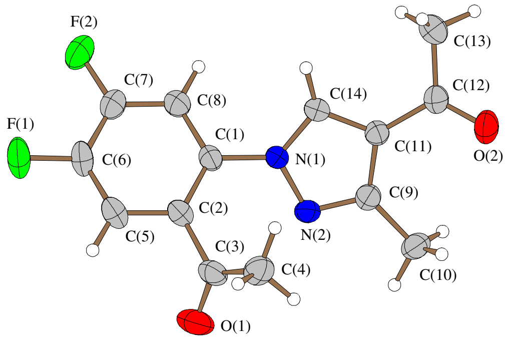

Figure 1 Molecular structure of compound **3**. Selected bond lengths (Å): C(1)–C(2) 1.388(3), C(1)–C(8) 1.390(3), C(1)–N(1) 1.424(2), C(2)–C(5) 1.400(3), C(2)–C(3) 1.514(3), C(3)–O(1) 1.214(3), C(3)–C(4) 1.491(3), C(5)–C(6) 1.366(3), C(6)–F(1) 1.355(2), C(6)–C(7) 1.378(3), C(7)–F(2) 1.344(3), C(7)–C(8) 1.373(3), N(1)–C(14) 1.347(2), N(1)–N(2) 1.370(2), N(2)–C(9) 1.325(3), C(9)–C(11) 1.431(3), C(9)–C(10) 1.490(3), C(11)–C(14) 1.379(3), C(11)–C(12) 1.464(3), C(12)–O(2) 1.220(3), C(12)–C(13) 1.500(3); torsion angles°: C(2)–C(1)–N(1)–N(2) 28.4(3), C(2)–C(1)–N(1)–C(14) –146.9(2), C(8)–C(1)–N(1)–N(2) –149.4(2), C(8)–C(1)–N(1)–C(14) 35.3(3).

demonstrates that, in the absence of O_2, the intermediate I_1 reacts to ketoester I_2, and the latter is destroyed by an acid under the reaction conditions to product **3**.

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[‡] *Crystal data for* **3**: at 173(2) K, a crystal of $C_{14}H_{12}F_2N_2O_2$ (0.80×0.40×0.40 mm) is monoclinic, $a = 8.667(1)$ Å, $b = 9.592(1)$ Å, $c = 16.090(2)$ Å, $\beta = 100.68(1)°$, $V = 1314.5(3)$ Å^3, space group $P2_1/c$, $Z = 4$, $d_{calc} = 1.406$ g/cm^3, $\mu = 0.114$ mm^{-1}, $F(000) = 576$. 4098 reflections were collected on a Siemens P4 diffractometer (MoKα radiation, $\theta/2\theta$-scan mode, $2.58 \le \theta \le 27.50°$), and 3017 independent reflections ($R_{int} = 0.0410$), were used in the crystal structure solution and refinement. The structure was solved by direct methods, the subsequent least-squares refinement located the positions of the remaining atoms in the electron density maps in an anisotropic approximation against F^2. The positions of hydrogens atoms were calculated geometrically and refined in a riding model. The refinement converged to $wR_2 = 0.1718$ and GOF = 1.021 for all reflections [$R_1 = 0.0601$ was calculated for 2108 observed reflections with $I > 2\sigma(I)$]. All calculations were performed with the SHELX program package.[7] The picture was drawn with the use of the DIAMOND program.[8]

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 217805. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2003.