Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 1996, **6**(1), 15–17
Mendeleev Communications

Benzimidazo[1,2-*a*]pyrazolo[1,5-*c*]quinazoline: a novel heterocyclic system

Galina N. Lipunova,* Galina A. Mokrushina, Emiliya B. Granovskaya, Olga M. Chasovskikh and Valerii N. Charushin

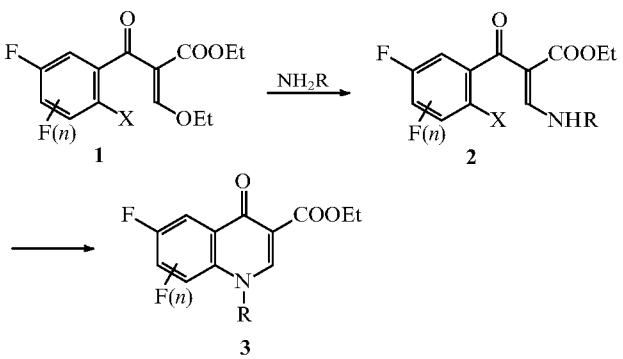
Organic Chemistry Department, Ural State Technical University, 620002 Ekaterinburg, Russian Federation. Fax: +7 3422 44 0458

Heating of ethyl 3-[β-(benzimidazol-2-yl)hydrazino]-2-(polyfluorobenzoyl)acrylates in acetonitrile with potassium fluoride or triethylbenzylammonium chloride leads to derivatives of novel heterocyclic systems of benzimidazo[1,2-*a*]pyrazolo-[1,5-*c*]quinazoline.

During recent years a number of highly effective antibacterials from the family of fluorinated derivatives of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid, known as 'fluoroquinolones', have found wide application.[1–4] One of the main synthetic approaches to these fluoroquinolones involves ethyl 3-ethoxy-2-(*m*-fluorobenzoyl)acrylates **1** as the key intermediates. The presence of an ethoxy group with good leaving ability enables one to introduce a variety of substituents at the N-1 position of fluoroquinolones **3** through interaction of **1** with primary amines followed by cyclization of the aroylacrylates **2** obtained into quinolones **3** (Scheme 1).[5,6]

Cyclization of acrylates **2** containing hydrazine substituents NHNHR (R = aryl or heteroaryl groups), instead of the amino group NHR, have not so far been studied. Meanwhile, introduction of a heteroaryl-substituted amino group at N-1 could open new possibilities in varying the structure of fluoroquinolones, as has recently been demonstrated by the reaction of 1-aminoquinolones with ketones.[7]

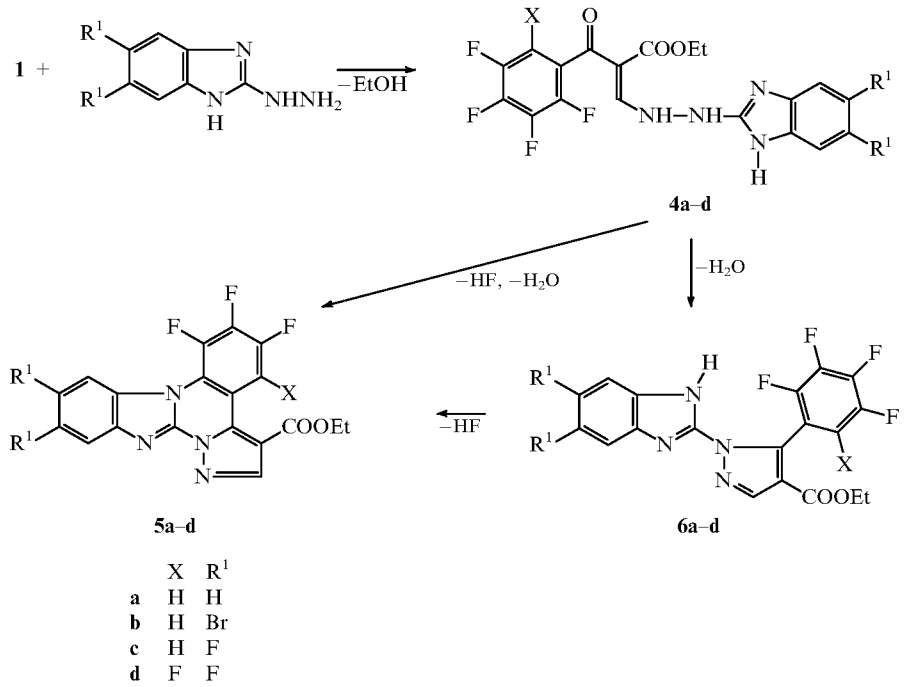
In order to obtain new derivatives of 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid bearing NH-heteroaryl groups at N-1, ethyl 3-[β-(benzimidazol-2-yl)hydrazino]-2-(polyfluorobenzoyl)acrylates **4a–d** were obtained and further transformations of **4a–d** into heterocyclic systems were studied. Compounds **4a–d** were obtained in high yields (80–90%) by means of the reaction of the corresponding tetra- or pentafluorobenzoyl acrylates **1** with benzimidazol-2-ylhydrazines in absolute toluene at room temperature.



Scheme 1

When the compounds **4a–d** were refluxed in acetonitrile with potassium fluoride or triethylbenzylammonium chloride for 4–6 h (*i.e.* under conditions usually reserved for the synthesis of fluoroquinolones[5,6]), derivatives of benzimidazo-[1,2-*a*]pyrazolo[1,5-*c*]quinazoline **5a–d**, a novel heterocyclic system, were formed in 45–65% yields (Scheme 2).

Evidence for the structure of compounds **5a–d** is provided by



	X	R^1
a	H	H
b	H	Br
c	H	F
d	F	F

Scheme 2

their IR, ^{1}H and ^{19}F NMR spectra, mass spectrometry data, as well as the X-ray analysis performed on compound **5a**.†

X-Ray crystallographic study of **5a** revealed that it consists of five aromatic rings and can be regarded as a fluorinated quinazoline condensed with pyrazole and benzimidazole ring systems. It is worth noting that all nitrogen and carbon atoms forming this polycyclic system lie almost in the same plane, with a maximal deviation of 0.237 Å, observed for C(11). Dihedral angles between benzimidazole, pyrimidine and benzene rings were found to be 6.4° and 13.3°, respectively. At the same time, the five-membered pyrazole ring is nearly coplanar with the six-membered pyrimidine ring (dihedral angle is only 3°).

It has been suggested that compounds **5** result from cyclization of intermediate pyrazol-1-yl substituted benzimidazoles **6**. Indeed, it has been found that under milder conditions (short-time heating of compounds **4a–d** in acetonitrile) 2-(5-polyfluorophenyl-4-ethoxycarbonylpyrazol-1-yl)benzimidazoles **6a–d** are formed in high yields, as follows from their ^{1}H, ^{13}C, ^{19}F NMR and mass spectrometry data. It is noteworthy that cyclization of acrylates **4** into benzimidazoles **6** is an extremely facile reaction; sometimes it occurs simultaneously on treating the compounds **1** with benzimidazolylhydrazines, thus yielding a mixture of products **4** and **6**. Further heating of compound **6a** in acetonitrile results in the formation of **5a**.‡

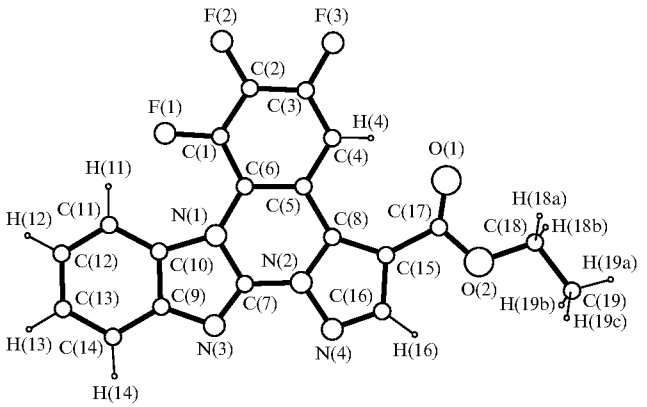


Figure 1 Molecular structure of compound **5a**.

† The authors are grateful to Dr. G. Alexandrov for the X-ray measurements. Numeration of atoms in Figure 1 does not correspond to IUPAC nomenclature.

‡ *Typical procedure for the synthesis of ethyl 3-[β-(benzimidazol-2-yl)hydrazino]-2-(polyfluorobenzoyl)acrylates* **4a–d**: Ethyl 3-ethoxy-2-(2,3,4,5-tetrafluorobenzoyl)acrylate (4 ml, 12 mmol) was added to a stirred suspension of benzimidazol-2-ylhydrazine (1.8 g, 12 mmol) in dry toluene and the reaction mixture was allowed to stand for 2 h at room temperature. The precipitate obtained was filtered off, washed with *n*-hexane and dried over Na_2SO_4 to give 4.1 g (80%) **4a**, mp 183–185 °C. Mp for other compounds/°C: **4b** 129–131, **4c** 208–210, **4d** 180–181.

Typical procedure for the synthesis of benzimidazo[1,2-a]pyrazolo-[1,5-c]quinazolines **5a–d**: (*a*) A solution of ethyl 3-[β-(benzimidazol-2-yl)hydrazino]-2-(tetrafluorobenzoyl)acrylate **4a** (1 g, 2.4 mmol) and potassium fluoride (0.27 g, 4.8 mmol) in 20 ml of acetonitrile was refluxed for 6 h. The precipitate obtained after cooling of the reaction mixture was filtered off, washed with water and recrystallized from acetonitrile to give 0.4 g (45%) of **5a**, mp 205–207 °C. Mp for other compounds/°C: **5b** 260 (from propan-2-ol); **5c** 221–222 (from acetonitrile); **5d** 215–216 (from acetonitrile); **6a** 193–195 (from acetonitrile); **6b** 165–167 (from propan-2-ol); **6c** 217–219 (from acetonitrile); **6d** 210–212 (from propan-2-ol).

(*b*) A solution of 2-(5-tetrafluorophenyl-4-ethoxycarbonylpyrazol-1-yl)benzimidazole **6a** (0.1 g, 0.25 mmol) and potassium fluoride (0.02 g, 0.3 mmol) in 5 ml of acetonitrile was refluxed for 4 h. The precipitate obtained after cooling of the reaction mixture was filtered off and recrystallized from acetonitrile to yield 0.09 g (77%) of **5a**, mp 205–207 °C. Mass spectrum, *m/z* 384(M^+, 100%), 356(28), 339(32), 312(18), 311(10.5), 285(7), 169(11.5), 102(6); IR, ν/cm^{-1} 3110, 3060, 1700, 1630, 1560, 1500; ^{1}H NMR ([$^2H_6$]DMSO): δ 1.4 t (3H, Me), 4.42 q (2H, OEt), 8.25–7.44 m (4H, arom.), 8.68 s (1H, H-6), 9.67 m (1H, arom.).

Experimental X-ray crystallographic data for **5a** were obtained on an 'Enraf-Nonius' diffractometer (λ MoKα, graphite monochromator θ-2θ scan, $2 < 2\theta < 44°$). The structure was solved by a direct method and refined by a full-matrix least-squares method in an anisotropic approximation to $R = 0.060$ ($R_W = 0.064$) for 1218 independent reflections with $F^2 > 2\alpha(F^2)$. $C_{19}H_{11}F_3N_4O_2$, monoclinic crystals, space group $P21/n$, $a = 7.798(3)$ Å, $b = 9.048(3)$ Å, $c = 23.010(7)$ Å, $\beta = 96.86(3)°$, $V = 1612(2)$ Å^3, $z = 4$. Full lists of bond angles, bond lengths and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. For details, see *Mendeleev Commun.*, 1996, Issue 1, 'Notice to Authors'.

References

1 *The Quinolones*, ed. T. V. Andriole, Academic Press, New York, 1988.
2 *The New Generation of Quinolones*, eds. C. Siporin, C. L. Heifetz and E. M. Domagala, Basel, New York, 1990.
3 *Quinolone Antibacterial Agents*, eds. D. C. Hooper and J. S. Wolfson, ASM, Washington, 1993.
4 G. A. Mokrushina, S. G. Alexeev, V. N. Charushin and O. N. Chupakhin, *Zh. Vses. Khim O-va im. D. I. Mendeleeva,* 1991, **34**, 447 (in Russian).
5 D. Bouzard, P. Di Cesare, M. Essiz, J. P. Jacquet, P. Remuzon, A. Weler, T. Oki and M. Masuyoshi, *J. Med. Chem.*, 1989, **32**, 537.
6 K. Grohe and H. Heitzer, *Liebigs Ann. Chem.*, 1987, 871.
7 O. N. Chupakhin, Yu. A. Azev, S. G. Alexeev, S. V. Shorshnev, E. Tsoi and V. N. Charushin, *Mendeleev Commun.*, 1992, 15.

Received: Moscow, 28th July 1995
Cambridge, 24th October 1995; Com. 5/05084G