# Benzimidazoles and related heterocycles
## 11.* A novel acid-catalyzed rearrangement in the system 3-benzoylquinoxalin-2(1*H*)-one—aldehyde—ammonium acetate as a simple and efficient route to 2-(imidazol-4-yl)benzimidazoles**

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A three-component condensation of 3-benzoylquinoxalin-2(1*H*)-one with 4-nitrobenzaldehyde and ammonium acetate in AcOH gives 2-[2-(4-nitrophenyl)-5-phenylimidazol-4-yl]benzimidazole *via* a rearrangement involving the fragment C(2)—C(3)—C(O)Ph of the quinoxaline system and the other two reagents, which supply the fragment —N=C(Ar)—NH— for constructing the imidazole ring. Possible pathways of this reaction are discussed.

**Key words:** 3-benzoylquinoxalin-2(1*H*)-one, aromatic aldehyde, ammonium acetate, acid-catalyzed rearrangement, 2-(imidazol-4-yl)benzimidazole, X-ray diffraction analysis.

Multicomponent reactions occupy a special place in modern organic synthesis and medicinal chemistry because they are highly economical and allow designing structurally complex and pharmacologically attractive compounds in a "one pot" manner simultaneously using three or more reagents.[2,3] At present, multicomponent reactions contribute greatly to the synthesis of complex and important organic molecules from simple and accessible starting materials and have become a powerful tool for the preparation of drugs.[4,5] Imidazoles and benzimidazoles are essential heterocycles found in many natural compounds and biological systems. Compounds containing an imidazole or benzimidazole fragment exhibit a variety of pharmacological properties and are crucial for biochemical processes.[6] The wide use of imidazole or benzimidazole derivatives in pharmacology is due to their hydrogen-bonding ability. They can act as both donors and acceptors and show high affinity for metals (Zn, Fe, and Mg) present on many active protein sites.[7] Various substituted imidazoles function as p38MAP[8] and B-Raf-kinase inhibitors,[9] glucagon receptors,[10] plant growth regulators,[11] therapeutic antibacterial[12] and antitumor[13] agents, and pesticides.[14] At the same time, benzimidazole derivatives are part of various biologically active compounds with antiviral, hypotensive, and antitumor activities.[15] Benzimidazole-containing compounds exhibit pronounced activity against such viruses as HIV,[16] herpes (VSV-1),[16,17] human cytomegalovirus (HCMV),[17] and flu virus.[18] Bisbenzimidazoles are DNA-crosslinking agents with antitumor activity.[19]

2,4,5-Trisubstituted imidazoles are mainly obtained by three-component cyclocondensation of 1,2-diketone, hydroxy ketone, or monooxime of an α-dicarbonyl compound with aldehydes and ammonium acetate. The synthesis may involve ionic liquids,[20] boiling acetic acid,[21] $H_2SO_4$-impregnated silica,[22] $InCl_3 \cdot 3H_2O$,[23] ammonium cerium nitrate (CAN),[24] $NiCl_2 \cdot 6H_2O/Al_2O_3$,[25] and microwave radiation.[26]

Earlier,[27—31] we have demonstrated that 3-aroyl- and 3-alkanoylquinoxalin-2(1*H*)-ones serve as suppliers of a two-carbon fragment in reactions with 1,2-diaminobenzenes. Due to the presence of the acyl group at the endocyclic imino fragment, these compounds behave like heteroanalogs of α-diketones yielding 3-substituted 2-(benzimidazol-2-yl)quinoxalines *via* contraction of the pyrazine ring.[31—33]

In the present work, we propose a simple and efficient route to 2-(imidazol-4-yl)benzimidazoles that involves a novel rearrangement in the system 3-benzoylquinoxalin-2(1*H*)-one (**1**)—4-nitrobenzaldehyde (**2**)—ammonium acetate (Scheme 1).

The reaction proceeds in boiling acetic acid for 19 h to give 2-[2-(4-nitrophenyl)-5-phenylimidazol-4-yl]benzimidazole (**3**). Its composition was determined from elemental analysis data. The structure was proved by IR and $^1$H NMR spectroscopy and X-ray diffraction.

The reaction was also successful with urea instead of ammonium acetate (as a nitrogen supplier for construct-

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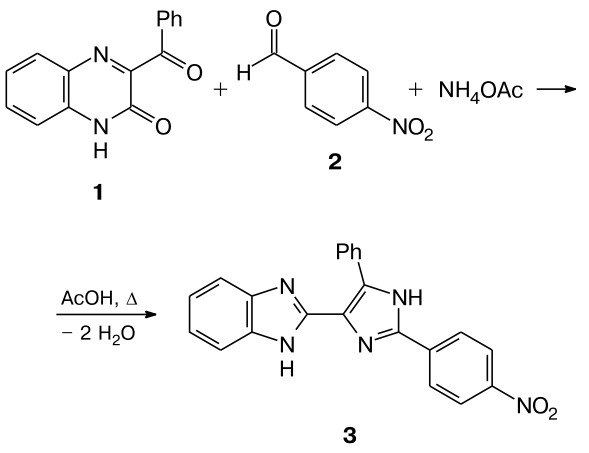
**Scheme 1**




ing the imidazole system) in boiling methanol in the presence of catalytic amounts of L-proline (0.3 mol.%) instead of acetic acid.

2-(Imidazol-4-yl)benzimidazole **3** forms monoclinic crystals (space group $P2_1/n$) and crystallizes in the protonated form (Fig. 1). The crystallographically independent part of the unit cell contains three molecules of acetic acid, one of which being present as the acetate anion. The crystal of compound **3** has a very peculiar system of intermolecular interactions; the distinctive features of its crystal packing will be discussed elsewhere.

The formation of the rearrangement product in the reaction of 3-benzoylquinoxalin-2(1*H*)-one (**1**) with 4-nitrobenzaldehyde (**2**) and ammonium acetate in AcOH can be represented by Scheme 2. Apparently, the initial step is the formation of spiro compound **B** from 3-benzoylquinoxalinone **1** and intermediate diamine **A**, which is

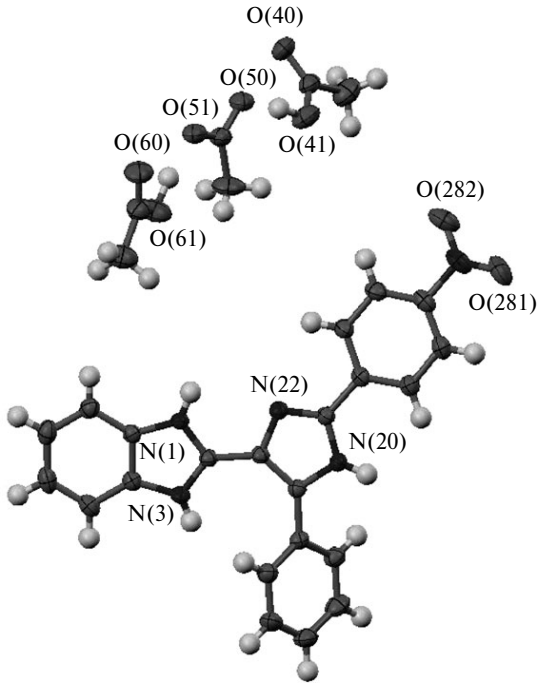
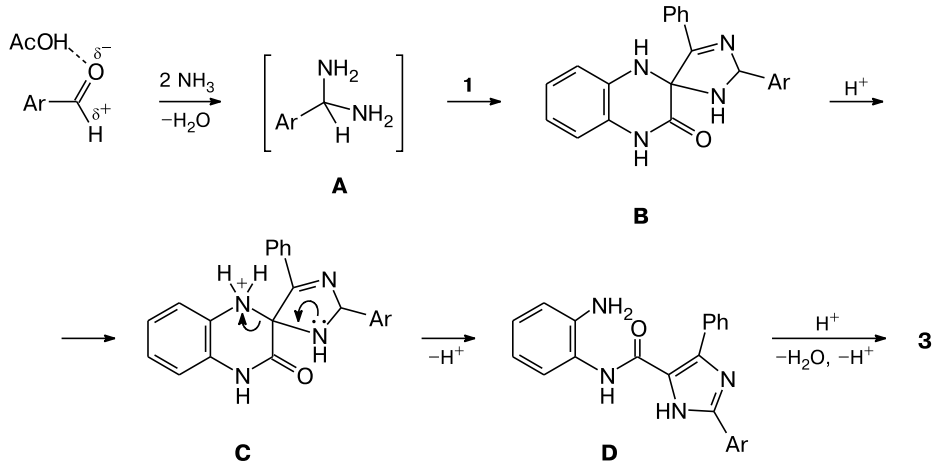



**Fig. 1.** Geometry of 2-[2-(4-nitrophenyl)-5-phenylimidazol-4-yl]benzimidazole (**3**) in the crystal with partial atomic numbering and thermal displacement ellipsoids for the non-hydrogen atoms ($p = 50\%$). The hydrogen atoms are represented by spheres of arbitrary radii.

followed by an acid-catalyzed *in situ* rearrangement involving (1) the opening of the pyrazine ring of the quinoxaline system with cleavage of the N(1)—C(2) bond in intermediate spiro compound **C** and (2) cyclization of imidazole derivative **D** into a benzimidazole system through a newly formed amino group and the carbamoyl C=O group (see Scheme 2).

**Scheme 2**




Ar = 4-$O_2NC_6H_4$

It should be noted that this reaction was successfully extended to other 3-aroylquinoxalin-2(1*H*)-ones and aromatic aldehydes in the presence of ammonium acetate, giving the corresponding 2-(imidazol-4-yl)benzimidazoles in good yields. These data provide evidence for the general character of the reaction under discussion and will be published elsewhere.

## Experimental

$^1$H NMR spectra were recorded on a Bruker-AVANCE-400 spectrometer (400.13 MHz). Chemical shifts δ are referenced to the residual signals of DMSO-$d_6$. IR spectra were recorded on a Vector-22 FTIR spectrometer (Bruker) in KBr pellets. Melting points were determined on a Boetius hot stage.

**2-[2-(4-Nitrophenyl)-5-phenylimidazol-4-yl]benzimidazole (3).** ***A.*** A solution of benzoylquinoxalinone **1** (0.2 g, 0.8 mmol), 4-nitrobenzaldehyde (**2**) (0.12 g, 0.8 mmol), and $NH_4OAc$ (0.62 g, 8 mmol) in AcOH (10 mL) was refluxed for 19 h, cooled to room temperature, and concentrated in a water aspirator vacuum. The residue was treated with 5% aqueous $NaHCO_3$. The precipitate that formed was filtered off, dried in air, refluxed in $Pr^iOH$, and filtered off hot. The yield of compound **3** was 0.22 g (73%), orange powder, m.p. 338—340 °C. Found (%): C, 69.37; H, 4.00; N, 18.29. $C_{22}H_{15}N_5O_2$. Calculated (%): C, 69.28; H, 3.96; N, 18.36. IR, ν/cm$^{-1}$: 3052, 2964, 2924, 2851, 1600, 1562, 1516, 1487, 1452, 1339, 853, 688, 586. $^1$H NMR, δ: 7.14—7.22 (m, 2 H, H(5), H(6) of benzimidazole); 7.44 (dd, 1 H, *p*-$H_{Ph}$, $J \approx 7.2$ Hz, $J \approx 7.2$ Hz); 7.52 (dd, 2 H, 2 *m*-$H_{Ph}$, $J \approx 7.2$ Hz, $J \approx 7.2$ Hz); 7.53—7.61 (m, 2 H, H(4), H(7) of benzimidazole); 8.08—8.16 (m, 2 H, 2 *o*-$H_{Ph}$); 8.41 (d, 2 H, $H_{Ar}$, $J = 9.2$ Hz); 8.44 (d, 2 H, $H_{Ar}$, $J = 9.2$ Hz). Recrystallization of compound **3** from aqueous acetic acid gave needle-like orange crystals of the formula $(C_{22}H_{16}N_5O_2)^+ \cdot CH_3CO_2^- \cdot 2CH_3CO_2H$, m.p. >350 °C. Found (%): C, 59.75; H, 4.76; N, 12.54. $C_{22}H_{15}N_5O_2 \cdot 3AcOH$. Calculated (%): C, 59.89; H, 4.81; N, 12.48. IR, ν/cm$^{-1}$: 3193, 3154, 3110, 2929, 2853, 1700, 1630, 1602, 1572, 1517, 1343, 1273, 1106, 756, 713, 452. $^1$H NMR, δ: 1.91 (s, 9 H, 3 Me); 7.15—7.19 (m, 2 H, H(5), H(6) of benzimidazole); 7.42 (dd, 1 H, *p*-$H_{Ph}$, $J = 7.2$ Hz, $J = 7.2$ Hz); 7.49 (dd, 2 H, 2 *m*-$H_{Ph}$, $J = 7.4$ Hz, $J = 7.6$ Hz); 7.54—7.58 (m, 2 H, H(4), H(7) of benzimidazole); 8.10 (br.d, 2 H, 2 *o*-$H_{Ph}$, $J \approx 7.4$ Hz); 8.39 (d, 2 H, $H_{Ar}$, $J = 9.0$ Hz); 8.43 (d, 2 H, $H_{Ar}$, $J = 9.0$ Hz).

***B.*** A solution of benzoylquinoxalinone **1** (0.2 g, 0.8 mmol), 4-nitrobenzaldehyde (**2**) (0.12 g, 0.8 mmol), and urea (0.19 g, 3.2 mmol) in AcOH (10 mL) was refluxed for 19 h. Workup of the reaction mixture was carried out as described above. The yield of compound **3** was 0.16 g (55%). Its melting point and spectroscopic characteristics are identical with those of the compound obtained according to procedure ***A***.

***C.*** A solution of benzoylquinoxalinone **1** (0.2 g, 0.8 mmol), 4-nitrobenzaldehyde (**2**) (0.12 g, 0.8 mmol), $NH_4OAc$ (0.62 g, 8 mmol), and L-proline (11 mol.%) in anhydrous MeOH (15 mL) was stirred at 65 °C for 19 h. Workup of the reaction mixture was carried out as described above. The yield of compound **3** was 0.18 g (59%). Its melting point and spectroscopic characteristics are identical with those of the compound obtained according to procedure ***A***.

**Single-crystal X-ray diffraction study** of compound **3** was performed at the Crystallographic Division of the Collective Use Center based on the Diffraction Investigations Laboratory of the A. E. Arbuzov Institute of Organic and Physical Chemistry (Kazan Research Center, Russian Academy of Sciences). The crystals of compound **3**, $(C_{22}H_{16}N_5O_2)^+ \cdot CH_3CO_2^- \cdot 2CH_3CO_2H$, are monoclinic; at 23 °C, the unit cell parameters are $a = 8.075(2)$ Å, $b = 21.991(5)$ Å, $c = 15.788(3)$ Å, $\beta = 101.076(2)°$, $V = 2752(1)$ Å$^3$, $Z = 4$, $d_{calc} = 1.356$ g cm$^{-3}$, space group $P2_1/n$. The unit cell parameters and the intensities of 30 008 reflections ($R_{int} = 0.0353$) were collected on a Bruker Smart Apex II CCD diffractometer (Mo-Kα radiation, graphite monochromator, $\lambda = 0.71073$ Å, ω scan mode; $-10 \le h \le 10$, $-28 \le k \le 28$, $-20 \le l \le 20$, $2.63° \le \theta \le 28.18°$). The number of independent reflections was 6465; the number of reflections with $I \ge 2\sigma(I)$ was 3642. An absorption correction was applied semiempirically with the SADABS program[34] ($\mu$(Mo) = 1.01 cm$^{-1}$). The structure was solved by the direct method and refined by the least-squares method isotropically and then anisotropically for all non-hydrogen atoms. The hydrogen atoms at the N(1), N(3), N(20), O(41), and O(61) atoms were located from difference electron-density maps and refined isotropically. The coordinates of the other H atoms were calculated from stereochemical considerations and refined using appropriate riding models. Final discrepancy factors are $R_1 = 0.0421$ and $wR_2 = 0.0934$ for 3642 independent reflections with $I > 2\sigma(I)$ and $R_1 = 0.0907$ and $wR_2 = 0.1131$ for all reflections; GOOF = 0.978, the number of parameters refined was 393. The maximum and minimum peaks in the difference electron-density maps are 0.130 and −0.109 e Å$^{-3}$, respectively. Experimental data were collected and edited, and the unit cell parameters were refined, with the APEX2 program.[35] All calculations used to solve and refine the structure were performed with the SHELXTL[36] and WinGX programs.[37] Intermolecular interactions were analyzed, and the molecular structures were drawn, with the PLATON program.[38] The atomic coordinates and thermal parameters for structure **3** have been deposited with the Cambridge Crystallographic Data Center (http://www.ccdc.cam.ac.uk; CCDC No. 779 105).

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