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A versatile one-step method for the synthesis of benzimidazoles from quinoxalinones and arylenediamines via a novel rearrangement

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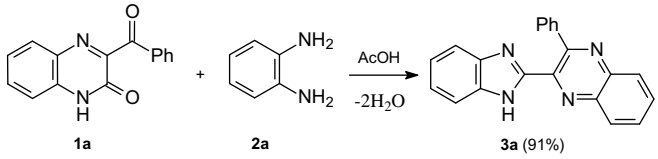
ABSTRACT

A highly efficient and versatile method for the synthesis of benzimidazoles has been developed on the basis of the novel ring contraction of 3-aroyl- and 3-alkanoylquinoxalin-2-ones with 1,2-arylenediamines.

Benzimidazole-containing compounds exhibit a wide range of biological properties. This class of heterocyclic systems has found commercial applications in several therapeutic areas as antiulcer, antihypertensive, antiviral,[1a,b] antifungal,[1c] antitumor,[1d–h] and antihistamine agents[1i] as well as anthelmintic agents in veterinary medicine.[1j–n] Medical chemists consider these heterocycles to be promising compounds.

Almost all the existing methods for the synthesis of benzimidazoles[1n,2a–j] have some synthetic shortcomings, such as rigid conditions and poor yields. Indeed, the development of new synthetic methods would be of considerable importance to chemists. The one-step method of Fokas and co-workers[3] is the most efficient method for the synthesis of benzimidazole derivatives, which involves the $Na_2S_2O_4$ reduction of *o*-nitroanilines in the presence of aldehydes in EtOH or other appropriate solvents. However, the method is restricted by its ability to synthesize a limited number of benzimidazole derivatives.

In this Letter, a direct, efficient, and convenient approach to the synthesis of 2-benzimidazolylquinoxalines is presented. The method is based on a new quinoxaline–benzimidazole rearrangement of 3-aroyl- **1a**,**f**[4] and 3-alkanoylquinoxalin-2-ones **1b–e**[5] under the action of 1,2-diaminobenzenes **2a–d** in acetic acid. Thus, the reaction of quinoxalin-2-one **1a** with 1,2-diaminobenzene **2a** in boiling acetic acid led to the corresponding 2-benzimidazolylquinoxaline **3a**[6] in 91% yield (Scheme 1).



Scheme 1.

Table 1 shows that a variety of quinoxalinones **1b–f** and 1,2-arylenediamines **2a–d** are compatible with these reaction conditions, producing diverse 2-benzimidazolyl-substituted quinoxalines in good yields. The reactions of 3-phenylacetylquinoxaline-2(1*H*)one **1b** with 3,4-diaminotoluene **2c**, or 4-nitro-1,2-phenylenediamine **2d**, produced a mixture of two isomers in almost equal amounts, as was evident from the ^{1}H NMR spectra of the crude products. Therefore, the quinoxalinone–benzimidazole rearrangement considered in this study is of rather general character.

On the basis of conventional chemistry of 1,2-phenylenediamines[7] and quinoxalinones[8a,b] it is reasonable to assume that the formation of 2-benzimidazolylquinoxaline **3** involves addition of the amino group of **2** at the C(3) atom of protonated quinoxalinone **1** as the first step. The next step involves nucleophilic attack of the second amino group of **2** at the benzoyl carbonyl group to form the spiro-quinoxaline derivative **A**. Then, ring contraction occurs with cleavage of the C(3)–N(4) bond in the intermediate tricyclic system **B** leading to formation of the final product **3** (Scheme 2). It should be noted that the formation of benzimidazolylquinoxalines can also be explained through initial attack of the amino

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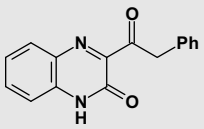
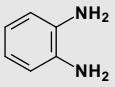
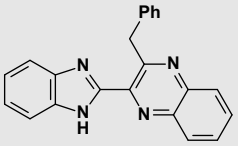
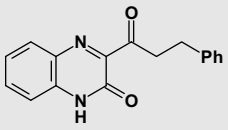
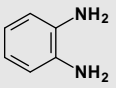
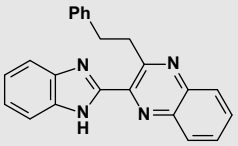
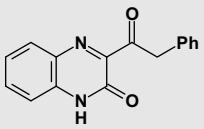
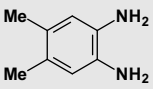
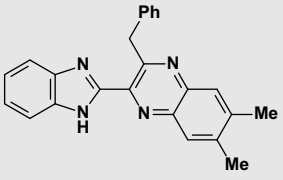
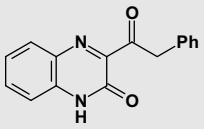
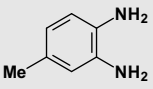
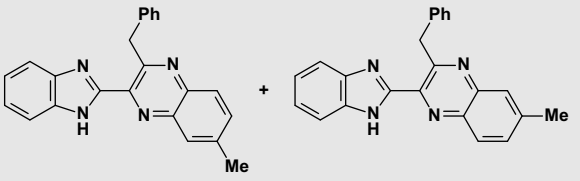
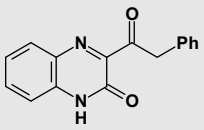
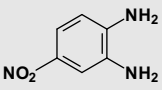
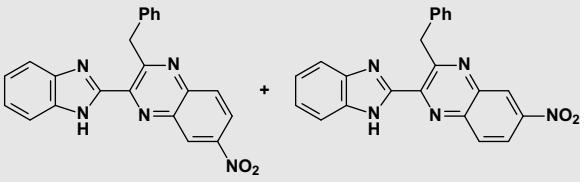
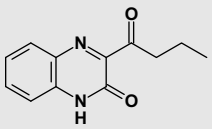
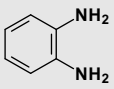
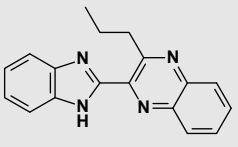
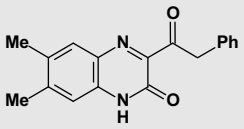
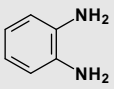
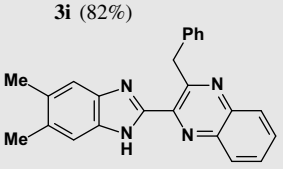
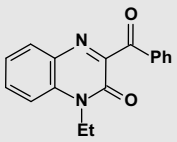
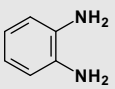
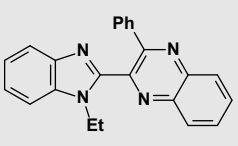
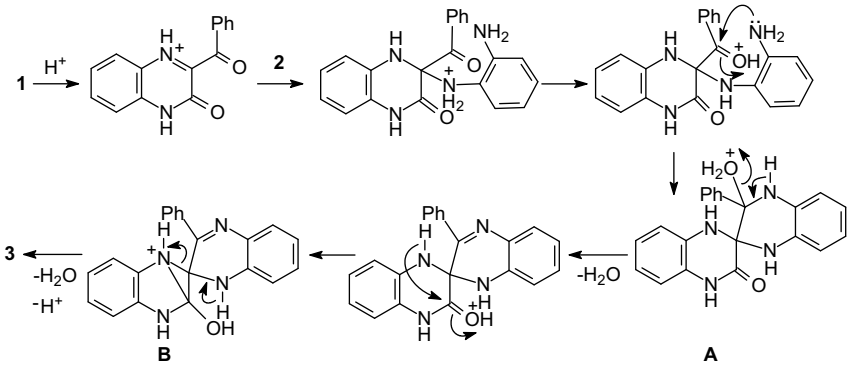
Table 1
The prepared 2-benzimidazolylquinoxalines

Entry	Substrate		Product (yield)
1	 **1b**	 **2a**	 **3b** (81%)
2	 **1c**	 **2a**	 **3c** (87%)
3	 **1b**	 **2b**	 **3d** (90%)
4	 **1b**	 **2c**	 **3e** (34%) **3f** (44%)
5	 **1b**	 **2d**	 **3g** (36%) **3h** (49%)
6	 **1d**	 **2a**	 **3i** (82%)
7	 **1e**	 **2a**	 **3j** (80%)
8	 **1f**	 **2a**	 **3k** (86%)



Scheme 2.

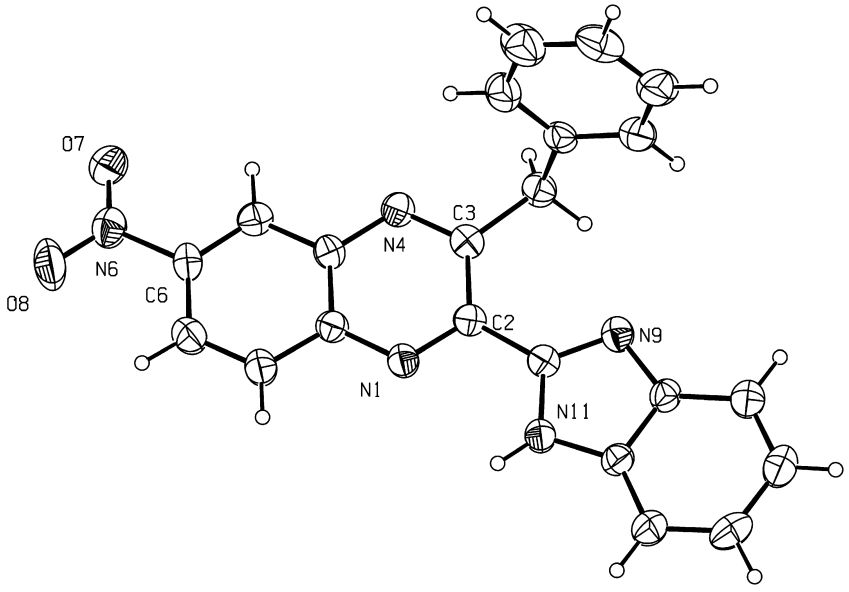


Figure 1. ORTEP drawing of compound **3h**.

group at the carbon atom of the ketone group. The rearrangement is then assumed to occur according to Scheme 2. This is confirmed indirectly by the formation of spiro-compounds with a structure similar to that of **A**, in the reactions of quinoxalinones with other binucleophilic compounds.[9] It has been shown that the investigated reaction does not proceed in neutral or aprotic solvents.

The structures of compounds **3** were deduced from the elemental analyses and ^{1}H and ^{13}C NMR data. The ^{1}H NMR spectral characteristics of 2-benzimidazolylquinoxalines are broad singlets due to protons H(5) and H(6) and multiplets for the protons H(4) and H(7) at δ 7.30–7.40 and δ 7.67–7.90 ppm, respectively.[10,11] The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. Initial fragmentation involved scission of the benzimidazole ring system.

The molecular structure of compound **3h** was confirmed by single-crystal X-ray analysis (Fig. 1).[12]

To summarize, we have reported an efficient and versatile one-step method for the preparation of a series of benzimidazoles as well as other imidazole-containing ring systems. This was accomplished by the quinoxalinone–benzimidazole rearrangement of 3-aroyl- and 3-alkanoyl-quinoxalin-2-ones in the presence of arylenediamines in acetic acid. This method makes it possible to synthesize N–H benzimidazoles as well as N- and C-substituted benzimidazoles. The reaction is readily applicable to large-scale synthesis. Application of this methodology to the synthesis of other heterocyclic ring systems is currently under investigation, and the results will be published in due time.

Acknowledgement

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6. Experimental procedure. A solution of 0.30 g (1.14 mmol) of 3-phenylacetylquinoxaline-2(1*H*)one **1b** and 0.12 g (1.14 mmol) of 1,2-phenylenediamine **2a** in 8 ml of acetic acid was heated under reflux for 2 h. After cooling to room temperature, the crystals of **3b** that precipitated were collected by suction filtration. Mp 224–225 °C. ^{1}H NMR (600 MHz, DMSO-d_6), δ 5.34 (2H, s, CH_2); 7.15 (1H, dd, H^p, J = 7.14, 7.24 Hz); 7.23 (2H, dd, 2H^m, J = 7.57, 7.58 Hz); 7.33–7.36 (2H, m, $H^{5'}$, $H^{6'}$); 7.35 (2H, d, 2H^o, J = 6.3 Hz); 7.78 (2H, br s, $H^{4'}$, $H^{7'}$); 7.91–7.96 (2H, m, H^6, H^7), 8.11–8.15 (1H, m, H^5 or H^8), 8.20–8.24 (1H, m, H^8 or H^5); ^{13}C NMR (150.93 MHz, DMSO-d_6), δ 41.84; 113.05; 120.86; 123.08; 124.97; 126.87; 129.03; 129.40; 129.46; 130.02; 131.31; 131.93; 135.35; 140.06; 140.59; 141.83; 143.49; 144.75; 150.24; 155.92. MS (EI), m/z (I(%)): $M^{+\cdot}$ 336(98); 335(100); 321(9); 259(6); 219(7); 218(19); 217(12); 216(7); 190(8); 168(40); 167(26); 154(7); 91(11); 90(7); 89(7); 77(6); 76(7). Anal. Calcd for $C_{22}H_{16}N_4$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.39; H, 4.60; N, 16.72.
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12. The X-ray diffraction data for the crystal structure of **3h** were collected on a Bruker AXS Kappa Apex diffractometer at 293 K. *Crystallographic data* for **3h**. $C_{22}H_{15}N_5O_2{\cdot}C_2H_6OS$, colorless prismatic crystal, formula weight 459.52, monoclinic, $C2/c$, a = 36.400(10), b = 6.2540(10), c = 26.552(4) Å, β = 131.60(3)°, V = 4520(2) Å^3, Z = 8, ρ_{calc} = 1.351 g cm^{-3}, μ (λ Mo Kα 0.71073 Å) = 0.180 mm^{-1}. $F(000)$ = 1920, reflections collected = 4627, unique = 4514, R_{int} = 0.0560, full-matrix least-squares on F^2, parameters = 308. Final indices R_1 = 0.0543, wR_2 = 0.1238 for 1455 reflections with $I > 2\sigma(I)$; R_1 = 0.2634, wR_2 = 0.1869 for all data, goodness-of-fit on F^2 = 0.902, largest difference in peak and hole (0.222 and −0.188 e Å^{-3}). Crystallographic data (excluding structure factors) for structure **3h** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 683079. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Deposited data may be accessed by the journal and checked as part of the refereeing process.