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Efficient synthesis of 2-(pyrazol-3-yl)benzimidazoles from 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-ones and hydrazine hydrate via a novel rearrangement

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ABSTRACT

A highly efficient method for the synthesis of 2-(pyrazol-3-yl)benzimidazoles has been developed on the basis of the novel ring contraction of 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-ones with hydrazine hydrate.

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Benzimidazoles exhibit a wide range of biological properties. This class of heterocyclic system has found commercial applications in several therapeutic areas such as antiulcer, antihypertensive, antiviral,[1a,b] antifungal,[1c] antitumor,[1d–h] and antihistamines[1i] as well as anthelmintic agents in veterinary medicine.[1j–n] Compounds possessing the benzimidazole moiety exhibit significant activity against viruses such as HIV,[1o,1p] herpes (HSV-1),[1q] human cytomegalovirus (HCMV),[1o,1p] and influenza.[1r]

Almost all existing methods for the synthesis of benzimidazoles[1n,2a–j] have some synthetic shortcomings, such as rigid conditions and poor yields of target products, which limit their scope. All these methods are essentially modifications of the classical Phillips–Ladenburg[3a,b] and Weidenhagen[4] reactions, which involve the condensation of *ortho*-phenylenediamine with carbonic acids or their derivatives or aldehydes. The method of Fokas and coworkers,[5] which is a modification of the Weidenhagen reaction is the most efficient for the synthesis of benzimidazoles, and 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 to the synthesis of a limited number of benzimidazole derivatives.

In this Letter, an efficient and convenient approach to the synthesis of 2-pyrazolylbenzimidazoles **3** is presented. The method is based on a new acid-catalyzed quinoxaline–benzimidazole rearrangement of 3′-aryl-1,2,3,4,4′,5′-hexahydrospiro[quinoxalin-2,5′-pyrazol]-3-ones **2a–f**, which are easily obtained from the reaction of the corresponding readily available 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-ones **1a–f**[6] with hydrazine hydrate in refluxing *n*-BuOH (Scheme 1). Thus, both the formation of spiroquinoxalinones **2a–f** and their rearrangement into the corresponding pyrazolylbenzimidazoles **3a–f** proceed in high yields (Schemes 1 and 2). As is evident from the structure of compounds 3a–f, the C(2)–C(3)=CH–C(O)–Ar fragment of quinoxalines **1a–f** and hydrazine hydrate is involved in the formation of the heterocyclic systems.

The structures of compounds **2a–f** and **3a–f** were deduced from their elemental analyses and ^{1}H NMR data.[7,8] The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. Initial fragmentation of compounds **2a–f** and **3a–f** involved scission of the benzimidazole and pyrazole ring systems.[7,8]

The ^{1}H NMR spectrum of the spiro compounds **2a–f** showed signals due to the phenyl and phenylene rings at 7.32–7.68 ppm and 6.68–6.89 ppm, respectively, three singlets at 7.04–7.97 ppm, 7.83–8.21 ppm, and 10.47–11.30 ppm, and two doublets at 3.01–3.11 ppm and 3.90–3.96 ppm ($^2J \sim 17.5$ Hz). The signals of the phenylene protons are shifted to stronger fields compared with the shifts of the protons of the phenylene ring (7.15–7.52 ppm) of quinoxalin-2(1*H*)-ones **1a–f**.[6] This demonstrates the involvement of the imine carbon atom in the reaction, with the nitrogen becoming

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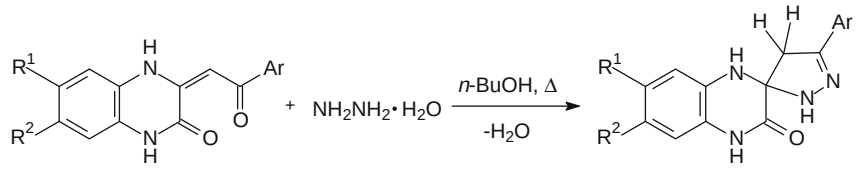
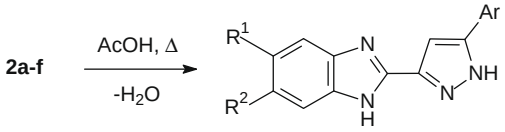


1a-f **2a-f**

Entry	R^1	R^2	Ar	Substrate	Product (yield)	M.p. (°C)
1	H	H	Ph	**1a**	**2a** (81%)	310-312
2	Me	Me	Ph	**1b**	**2b** (76%)	237-240
3	H	Cl	Ph	**1c**	**2c** (64%)	243-246
4	NO_2	H	Ph	**1d**	**2d** (73%)	235-238
5	H	H	*p*-MeC_6H_4	**1e**	**2e** (77%)	230-231
6	H	H	*p*-ClC_6H_4	**1f**	**2f** (73%)	235-237

Scheme 1.



3a-f

Entry	R^1	R^2	Ar	Substrate	Product (yield)	M.p. (°C)
1	H	H	Ph	**2a**	**3a** (99%)	316-317
2	Me	Me	Ph	**2b**	**3b** (99%)	264-265
3	H	Cl	Ph	**2c**	**3c** (98%)	305-307
4	NO_2	H	Ph	**2d**	**3d** (96%)	295-296
5	H	H	*p*-MeC_6H_4	**2e**	**3e** (99%)	309-310
6	H	H	*p*-ClC_6H_4	**2f**	**3f** (85%)	343-345

Scheme 2.

an electron-donating amine nitrogen. IR spectroscopy also confirmed the structure of spiro-compounds **2a–f**. The ^{1}H NMR spectral characteristics of pyrazolylbenzimidazoles **3a–f** are multiplets for protons H(4) and H(7) and broad singlets due to protons H(5) and H(6) at 7.21–7.23 ppm and 7.50–7.60 ppm, respectively.[9a,b]

The molecular structures of spiro-compound **2e** and pyrazolylbenzimidazole **3a** were unambiguously confirmed by single-crystal X-ray analyses (Fig. 1)[10] and (Fig. 2).[11]

On the basis of the known chemistry of hydrazines,[12a,b] ketones, 13a,b and quinoxalinones[14a,b] it is reasonable to assume that the first stage of the reaction mechanism involves the addition of hydrazine to the carbonyl group of the 3-arylacylidene fragment of quinoxalin-2(1*H*)-one **1** with the formation of intermediate **A** which can undergo tautomerization with intermediate **B**. The next step involves nucleophilic attack of the amino group on C-3 of the quinoxalin-

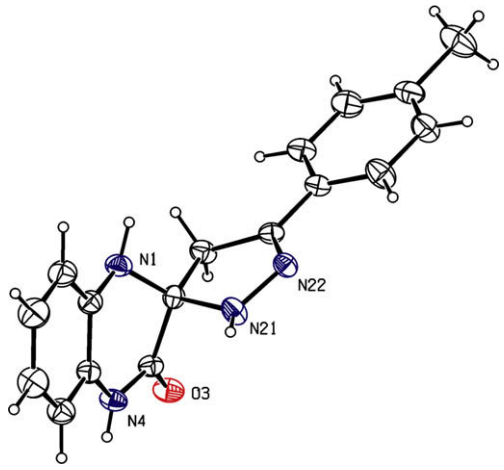


Figure 1. ORTEP drawing of **2e**. Displacement ellipsoids are drawn at the 30% probability level. H atoms are represented by circles of arbitrary size.

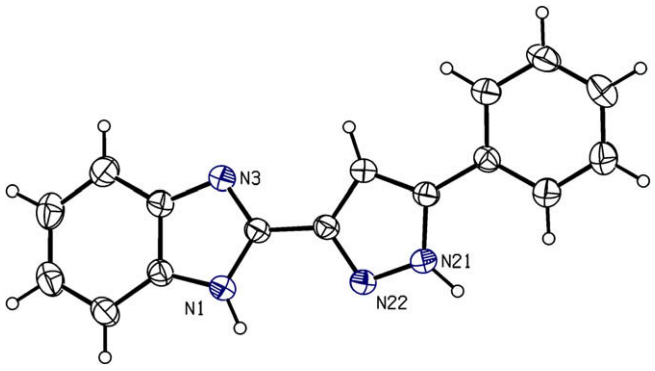
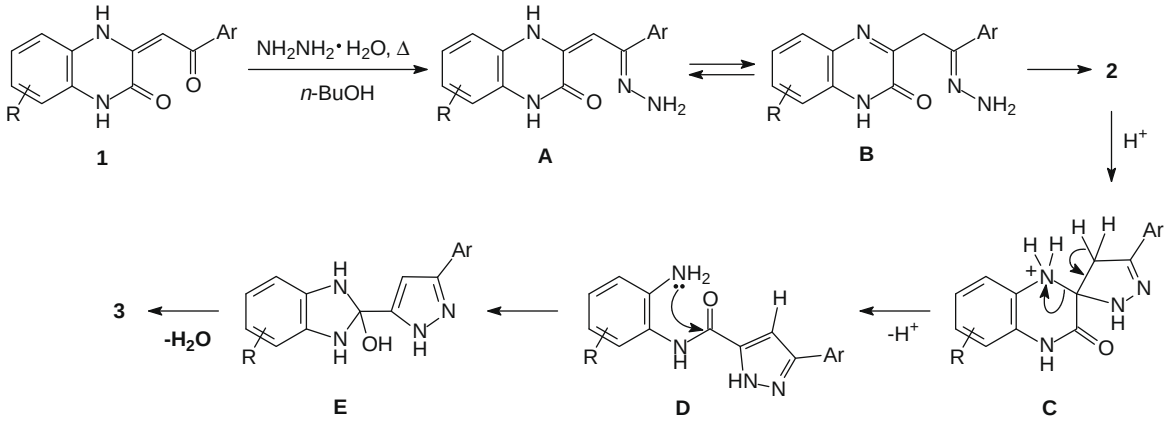


Figure 2. ORTEP drawing of **3a**. Displacement ellipsoids are drawn at the 30% probability level. H atoms are represented by circles of arbitrary size.



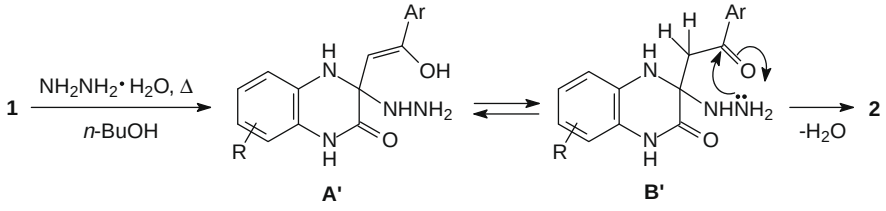
Scheme 3.

2(1*H*)-one to form the spiroquinoxaline derivative **2**. Rearrangement of the spiroquinoxaline is then assumed to occur according to Scheme 3, which proceeds by cascade reactions involving: (a) acid-catalyzed ring-opening of spiro-compound **C** with the formation of pyrazolo derivative **D**, (b) intramolecular nucleophilic attack by the amino moiety on the carbonyl group leading to the formation of hydroxy derivative **E**, and (c) elimination of water to give the final product **3**. It was shown that the reaction does not proceed in neutral or aprotic solvents.

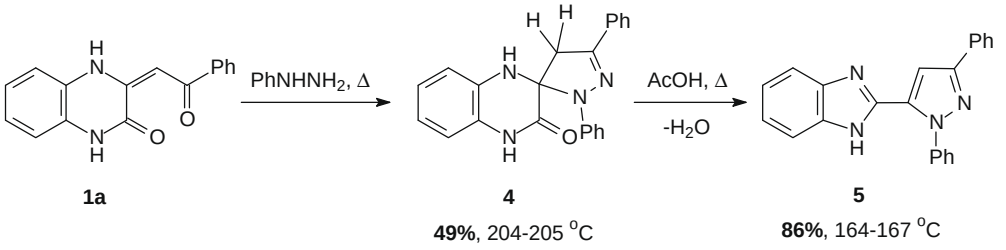
It should be pointed out that the formation of spiroquinoxaline derivative **2** can also be explained via Michael addition of hydrazine to the partially positive C(3) atom of the quinoxalin-2(1*H*)-one **1** in the first stage of the reaction with the formation of intermediate **A**′ which can tautomerize with intermediate **B**′. Cyclization then occurs through nucleophilic attack of the amino moiety on the carbonyl group of the 3-arylacylidene fragment of **B**′ (Scheme 4).

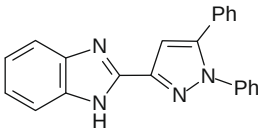
It is worth noting that the reaction of phenylhydrazine with 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-one **1a** proceeds similarly to the reaction with hydrazine hydrate. This involves the formation of spiro-compound **4**, which rearranges into pyrazolylbenzimidazole **5**, and not the other possible regioisomer **5a**, in boiling acetic acid (Scheme 5).

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 via a novel quinoxalinone–benzimidazole rearrangement of 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-ones on exposure



Scheme 4.





Scheme 5.

to hydrazine hydrate. 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 course.

Acknowledgment

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6. For the synthesis of **1a** and **1f**, see: Amer, A.; Ventura, M.; Zimmer, H. *J. Heterocycl. Chem.* **1983**, *20*, 359. Quinoxalinones **1b–e** were prepared by the method used for **1a**. Mp 298–299 °C (**1b**); 302–303 °C (**1c**); 304–306 °C (**1d**); 252–253 °C (**1e**).
7. *Typical procedure for the preparation of* **2**. A suspension of 3-phenylacylidene-3,4-dihydroquinoxalin-2(1*H*)-one **1a** (0.13 g, 0.5 mmol) and hydrazine monohydrate (0.23 g, 5 mmol) (90%) in *n*-BuOH (10 mL) was heated at reflux for 16 h. After cooling to room temperature and standing overnight, the crystals of **2a** that precipitated were collected by suction filtration, washed with EtOH (2 × 5 mL), dried in air, and recrystallized from CH_3CN, to give 0.07 g (51%) of **2a**. The filtrate was evaporated to one-half of the initial volume and left overnight at room temperature. The crystals of **2a** that precipitated were collected by suction filtration, washed with EtOH (2 × 5 mL), dried in air, and after recrystallization from CH_3CN gave additionally 0.04 g (30%) of **2a**: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 3.03 (1H, d, CH_AH_B, J_{AB} = 17.4 Hz); 3.93 (1H, d, CH_AH_B, J_{AB} = 17.4 Hz); 6.70 (1H, dd, H^6, J = 7.5; 7.5 Hz); 6.74 (1H, d, H^8, J = 7.2 Hz); 6.84 (1H, dd, H^7, J = 7.5; 7.5 Hz); 6.85 (1H, d, H^5, J = 7.5 Hz); 7.32 (1H, br s, NH); 7.35 (1H, d, H^p, J = 7.5 Hz); 7.42 (2H, dd, $2H^m$, J = 7.9; 7.2 Hz); 7.67 (2H, d, $2H^o$, J = 7.2 Hz); 7.98 (1H, br s, NH); 10.64 (1H, br s, NH). IR (KBr) cm^{-1}: 3445, 3318, 3261, 3080, 2960, 1664, 1617, 1604, 1504, 1446, 1413, 1377, 1356, 1312, 1218, 1062, 1002, 915, 871, 755, 735, 687. MS (EI), *m/z* (%): 278 (32) M^+, 250 (27), 249 (11), 221 (17), 202 (32), 172 (18), 171 (15), 161 (12), 160 (52), 133 (17), 131 (100), 119 (13), 118 (19), 117 (10), 114(16). Anal. Calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.83; H, 4.92; N, 20.19.
8. *Typical procedure for the preparation of* **3**. A solution of spiroquinoxalinone (0.2 g, 0.7 mmol) **2a** in acetic acid (10 mL) was heated at reflux for 8 h. The reaction mixture was evaporated in vacuo to give 0.19 g (99%) of **3a** which was analytically pure. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 7.22 (2H, m, H^7, H^4); 7.33 (1H, s, $H^{4'}$); 7.40 (1H, dd, H^p, J = 7.2; 7.5 Hz); 7.51 (2H, dd, $2H^m$, J = 7.8; 7.2 Hz); 7.60 (2H, br.s, H^5, H^6); 7.87 (2H, d, $2H^o$, J = 7.5 Hz). IR (KBr) cm^{-1}: 3427, 3212, 3167, 3110, 3026, 2605, 2526, 1693, 1566, 1499, 1456, 1438, 1419, 1363, 1280, 1267, 1196, 1025, 968, 889, 806, 762, 749. MS (EI), *m/z* (%): 260 (100) M^+, 232 (11), 231 (33). Anal. Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.41; H, 4.58; N, 21.50.
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10. The X-ray diffraction data for crystals of **2e** were collected on a Smart Apex II CCD diffractometer at 296 K. Crystallographic data for **2e**. $C_{17}H_{16}N_4O$, colorless prism, formula weight 292.34, orthorhombic, $P\ 2_12_12_1$, a = 5.609(3), b = 9.854(5), c = 27.272(15) Å, V = 1507.4(1) Å^3, Z = 4, ρ_{calc} = 1.288 g cm^{-3}, $\mu(\lambda$Mo K$\alpha)$ = 0.84 cm^{-1}. $F(0\,0\,0)$ = 616, reflections collected = 16658, unique = 3574, R(int) = 0.1120, full-matrix least-squares on F^2, parameters = 213, restraints = 0. Final indices R_1 = 0.0352, wR_2 = 0.0544 for 1358 reflections with $I > 2\sigma(I)$; R_1 = 0.0676, wR_2 = 0.1481 for all data, goodness-of-fit on F^2 = 0.884, largest difference in peak and hole (0.099 and −0.128 e Å^{-3}). Crystallographic data (excluding structure factors) for the structure **2e** reported in this Letter have been deposited at the Cambridge Crystallographic Data Centre with supplementary Publication Number CCDC 724170. Copies of the 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).
11. The X-ray diffraction data for crystals of **3a** were collected on a Bruker AXS Smart Apex II CCD diffractometer at 296 K. Crystallographic data for **3a**. $C_{16}H_{12}N_4$, $2(C_2H_4O_2)$, pink prism, formula weight 380.40, monoclinic, $P\ 2_1/n$, a = 7.1835(4), b = 14.8945(9), c = 18.2328(12) Å, β = 92.504(1)°, V = 1948.9(2) Å^3, Z = 4, ρ_{calc} = 1.296 g cm^{-3}, $\mu(\lambda$Mo K$\alpha)$ = 0.92 cm^{-1}. $F(0\,0\,0)$ = 800, reflections collected = 21441, unique = 4624, R(int) = 0.0227, full-matrix least-squares on F^2, parameters = 271, restraints = 0. Final indices R_1 = 0.0517, wR_2 = 0.1969 for 3339 reflections with $I > 2\sigma(I)$; R_1 = 0.0684, wR_2 = 0.2471 for all data, goodness-of-fit on F^2 = 0.851, largest difference in peak and hole (0.198 and −0.141 e Å^{-3}). Crystallographic data (excluding structure factors) for the structure **3a** reported in this Letter have been deposited at the Cambridge Crystallographic Data Centre with supplementary Publication Number CCDC 724169. Copies of the 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).
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