Tetrahedron Letters 55 (2014) 4319–4324

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Quinoxalinone–benzimidazole rearrangement: an efficient strategy for the synthesis of structurally diverse quinoline derivatives with benzimidazole moieties

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ARTICLE INFO

Article history:
Received 30 March 2014
Revised 17 May 2014
Accepted 5 June 2014
Available online 12 June 2014

Dedicated to the 80th anniversary of Academician Oleg Nikolaevich Chupakhin

Keywords:
3-(2-Aminophenyl)quinoxalin-2(1*H*)-one
Ring contractions
Ring formation
Novel rearrangement
4-(Benzimidazol-2-yl)quinolines

ABSTRACT

A novel and efficient procedure for the synthesis of structurally diverse benzimidazolylquinolines has been realized through a new acid-catalyzed quinoxalinone–benzimidazole rearrangement of the spiro-quinoxalinone derivatives formed in situ from the reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones and different ketones.

Quinolines and their derivatives are very important biological compounds that occur widely in natural products, examples of which demonstrate antimalarial, anti-asthmatic, antihypertensive, and antibacterial activities, and tyrosine kinase inhibition.[1] Quinoline derivatives can also be useful ligands and functional materials,[2] and some of them have been applied in the study of bioorganic and bioorgano-metallic processes.[3] Therefore, quinoline derivatives have become the synthetic targets of many organic and medicinal chemists, and a variety of methods for their synthesis, such as the Skraup, Doebner–Von Miller, Friedländer, and Combes methods have been developed and extended.[4] For example, the Friedländer reaction is generally carried out either by refluxing an aqueous or alcoholic solution of the reactants in the presence of a base, or by heating a mixture of the reactants at 150–220 °C in the absence of a catalyst.[5] In order to improve the generality of the Friedländer method, Bronsted acids such as hydrochloric acid,[6] *p*-toluenesulfonic acid,[7] dodecylphosphonic acid,[8] and sulfuric acid modified PEG-6000[9] have been employed. Modified methods, using Lewis acids,[10] inorganic salts,[11] and ionic liquids,[12] have also been reported for this reaction. However, the principal shortcomings (such as long reaction times, harsh reaction conditions, or the use of volatile, and hazardous organic solvents) of these conventionally named routes do not allow them to be used for synthesizing quinoline derivatives with various types of the heterocyclic ring systems directly attached to the quinoline core.

We have previously shown[13a–p] that due to the presence of an imine function between the C3 and N4 atoms of the pyrazine ring, the derivatives of quinoxalin-2(1*H*)-one **Q** depend on the nature of substituents R^1 at position 3; they behave like imino analogs of α-chloroketones [in the case of R^1 = CH(Cl)Ph],[13a] α-aminoketones [in the case of R^1 = $CH(NH_2)Ph$],[13b] α-azidoketones [in the case of R^1 = $CH(N_3)(CH_2)_nPh$],[13c] α-diketones [in the case of R^1 = C(O)Ar, C(O)Alk],[13d–k] simple ketones [in the case of R^1 = Me],[13l] and β-diketones [in the case of R^1 = $CH_2C(O)Ar$],[13m,n] and are subject to novel acid-catalyzed rearrangement[13p,q] in reactions with various *N*-nucleophiles. In these cases they result in 2-heteroaryl-substituted benzimidazole derivatives (Scheme 1).

Following the results reported in our previous papers[13a–n] on the new rearrangement of quinoxalin-2(1*H*)-one derivatives,[13p,q] we assumed that 3-(2-aminophenyl)quinoxalin-2(1*H*)-one (**1**) could be used as a heteroanalog of the *ortho*-amino aromatic aldehydes employed in the Friedländer reaction, with the ketones

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http://dx.doi.org/10.1016/j.tetlet.2014.06.023
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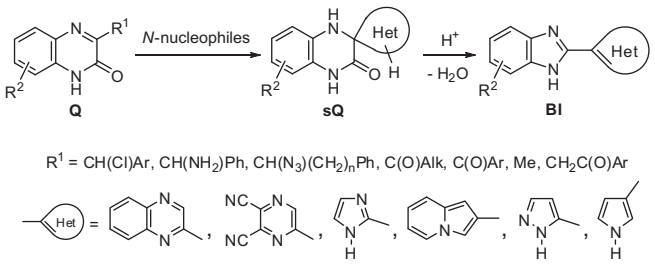
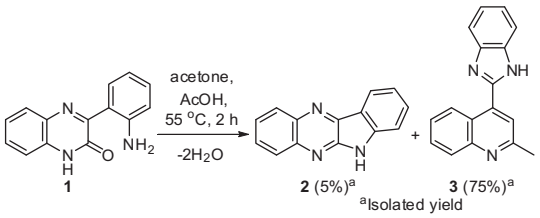


Scheme 1. Common presentation of the rearrangement for the synthesis of 2-heteroaryl-benzimidazoles.



Scheme 2. The reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-one derivative (**1**) with acetone.

bearing an active α-methylene functionality, capable of providing a two-carbon fragment in the construction of the quinoline system. We assumed that the presence of a quinoline fragment with at least one mobile hydrogen atom at position 3 of the quinoxalin-2(1*H*)-one system was presumably the key factor for the acid-catalyzed rearrangement as in the previous cases,[13] and would make it possible to synthesize 4-(benzimidazol-2-yl)quinolines **3** and **5**. Because of the importance of these heterocycles and significant enhancement expectations in their biological activity in the presence of two different heterocyclic motifs in a single molecule,[14] we became interested in the synthesis of quinoline–benzimidazole conjugates. Herein, we report the facile synthesis of 4-(benzimidazol-2-yl)quinolines via the one-pot condensation of 3-(2-aminophenyl)quinoxalin-2(1*H*)-one (**1**) with various carbonyl compounds.

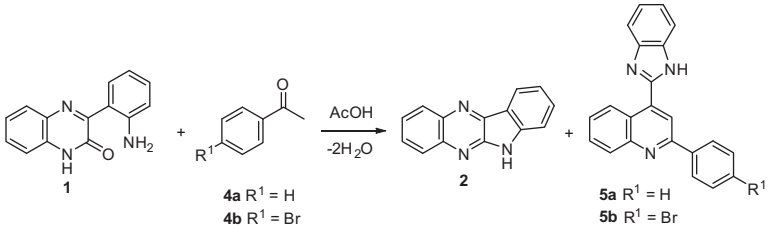
To optimize the process, we initially carried out the reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-one (**1**) with acetone in acetic acid with various ratios of reagents and different reaction times. Regardless of the molar ratio of the reagents (1:32, 1:16, 1:8, 1:4; **1**:acetone) and the reaction time (6, 4 or 2 h) the reaction proceeded in the same way with the formation of an ~85% yield of the crude product, which on the basis of the ^{1}H NMR spectrum contains ~90% of the quinoline 3 and ~10% of the quinoxaline derivative 2 (Scheme 2).

The quinoline **3** is formed via the rearrangement, whereas 6*H*-indolo[2,3-*b*]quinoxaline (**2**) is the result of intramolecular cyclocondensation of the quinoxaline derivative **1**. The optimal temperature for this reaction corresponds approximately to the boiling temperature of acetone (55 °C). This temperature appears to be optimal for the reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-one (**1**) with acetophenone (**4a**) and 4-bromoacetophenone (**4b**). As can be seen from Table 1, in these cases, the optimal ratio was 1:2 (**1**:**4a** and **1**:**4b**) when the reactions were carried out for five hours (entries 4 and 9), because when the ratio of the reagents was 1:1, the yield of compound 2 increased and there was a decrease in the overall yield of the mixture of compounds **2** and **5** (entries 1, 6 and 7). When the ratio of the starting compounds was 1:10 or 1:5 (entries 5 and 10), despite the satisfactory yield of the desired products, difficulties occurred during purification of the final products.

To explore the scope and limitations of the reaction, the procedure was extended to various acetophenones **4**. As indicated in Table 2, the reactions proceeded very efficiently, and led to the formation of the corresponding 4-(benzimidazol-2-yl)quinolines **5a**–**f** as the major and 6*H*-indolo[2,3-*b*]quinoxaline (**2**) as minor products.

Based on the known chemistry of amines,[16] enolizable ketones,[17] enamines,[18] quinoxalinones,[19] and the previous reports,[13a–m] a plausible mechanism for the formation of 4-(benzimidazol-2-yl)quinolines **5** is proposed (Scheme 3). The reaction starts with the condensation of the ketone with 3-(2-aminophenyl)quinoxalin-2(1*H*)-one (**1**) to form imine **A**, which transforms into the intermediate **B** by tautomerization. Subsequently, the intermediate **B** is easily cyclized via intramolecular nucleophilic

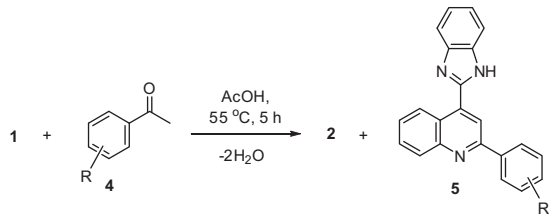
Table 1
Optimization of the reaction conditions

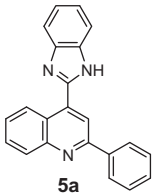
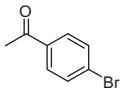
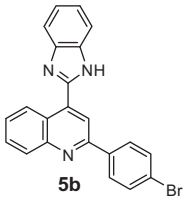
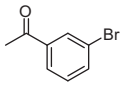
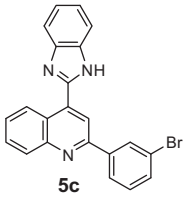
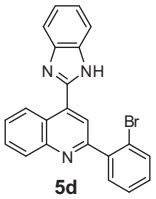
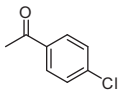
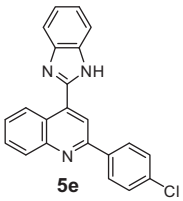
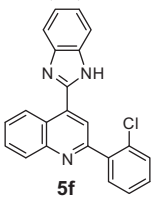


Entry	Substrate	Ratio of **1**:**4**	Temp (°C)	Time (h)	Ratio of products[a]	Total yield[b] (%)
						2 + **5**
1	**4a**	1:1	55	2	**2** + **5a** (20:80)	54
2	**4a**	1:2	Reflux	2	**2** + **5a** (15:85)	52
3	**4a**	1:2	55	2	**2** + **5a** (12:88)	75
4	**4a**	1:2	55	5	**2** + **5a** (15:85)	95
5	**4a**	1:10	55	5	**2** + **5a** (15:85)	80
6	**4b**	1:1	55	2	**2** + **5b** (8:92)	40
7	**4b**	1:1	55	6	**2** + **5b** (8:92)	46
8	**4b**	1:2	55	2	**2** + **5b** (5:95)	79
9	**4b**	1:2	55	5	**2** + **5b** (4:96)	86
10	**4b**	1:5	55	5	**2** + **5b** (4:96)	72

[a] Estimated on the basis of the ^{1}H NMR spectra of the reaction mixture.
[b] Yields based on the isolated mixture of products.

Table 2
Reaction of 3-(2-aminophenyl)-quinoxalin-2(1*H*)-one **1** with acetophenones **4a–f**[15]



Entry	Acetophenone **4**	Products, yield (%)[a]	Mp (°C) **5**
1	 **4a**	**2** +  **5a** (6) (80)	230–232
2	 **4b**	**2** +  **5b** (4) (76)	228–231
3	 **4c**	**2** +  **5c** (4) (78)	223–225
4	 **4d**	**2** +  **5d** (4) (73)	248–250
5	 **4e**	**2** +  **5e** (4) (77)	239–241
6	 **4f**	**2** +  **5f** (4) (71)	245–246

[a] Isolated yields.

addition to give the spiro-quinoxaline derivative **C**. The rearrangement of the spiro-quinoxalinone **C** is then assumed to occur via cascade reactions involving: (a) ring-opening with cleavage of the C3–N4 bond in the spiro-compound **D** with the formation of the intermediate quinoline derivative **E**, (b) intramolecular nucleophilic attack by the amino group on the carbonyl group with the formation of the hydroxy-derivative **F**, and (c) the elimination of water leading to formation of the final product **5**. All the stages of the reaction involve acid-catalyzed processes.

As can be seen, this chemistry is not limited to acetone and acetophenones with various substituents; a ketone with an ester group, viz. ethyl acetoacetate (**6**) was also an acceptable substrate (Scheme 4). The latter case makes it possible to construct the benzimidazolo[2,1-*a*]pyrrolo[3,4-*c*]quinolinone system **8**,[20] which is difficult to access by other known methods.

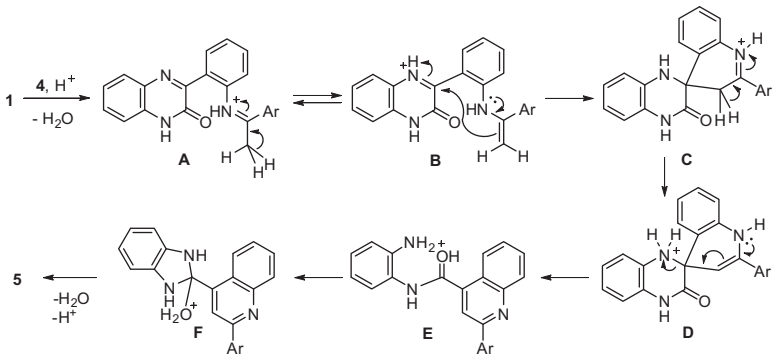
All the compounds synthesized (**3**, **5a–f**, and **8**) were characterized by NMR, MS, and IR spectroscopy and elemental analyses. For example, the mass spectra of quinolines **5e** and **5b** displayed characteristic molecular ion peaks at 356 for M^+ ([^{35}Cl]) and 358 for M^+ ([^{37}Cl]) (Fig. 1a) and 400 for M^+ ([^{79}Br]) and 402 for M^+ ([^{81}Br]) (Fig. 1b), respectively, consistent with the molecular structures.

The ^{1}H NMR spectrum of **5e** contains three groups of characteristic signals for the benzimidazole, quinoline, and 4-ClC_6H_4 fragments. In this case, the protons of the benzene ring of benzimidazole resonate as a strongly coupled AA′BB′ spin system as multiplets at δ 7.29–7.37 and δ 7.70–7.78 due to H5+H6 and H4+H7 of the benzimidazole fragment, respectively. The proton of the NH group of the benzimidazole moiety resonates at δ 13.36 as a characteristic singlet. The quinoline system is characterized by two doublet of doublet of doublets at δ 7.68 and δ 7.84, one doublet at δ 8.14, one doublet of doublets at δ 9.14, and one singlet at δ 8.46 due to H6, H7, H8, H5, and H3 of the quinoline fragment. The protons of the 4-chlorophenylene ring resonated as a simplified case of the AA′XX′ spin system with two doublets at δ 7.60 and δ 8.30. The ^{1}H NMR spectra of **5a–d**,**f** were very similar to that of **5e**, except for the signals of the protons of the phenyl groups.

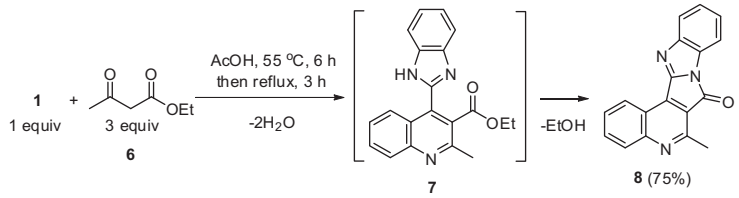
The structures of the 2-methyl- (**3**) and 2-phenyl- (**5a**) 4-(benzimidazol-2-yl)quinolines were further determined by X-ray crystallographic analysis (Fig. 2).[21–23]

The X-ray crystallographic analysis shows that both crystal units of **3** and **5a** include one water molecule and the geometrical parameters of the heterocycles of both molecules **3** and **5a** are equivalent within experimental error. According to the PLATON program calculations, the dihedral angles between the benzimidazole and quinoline planes in molecules **3** and **5a** are 56.47(8) and 50.5(1)°, respectively.[24] The slight decrease of this angle in **5a** could be due to the presence of the phenyl substituent, thus increasing the delocalization of the π-system of the benzimidazole and quinoline heterocycles. In spite of this fact, the dihedral angle between the quinoline and phenyl planes in molecule **5a** is significant and equal to 30.6(1)°. We only found about 50 structures in the Cambridge Structural Database[25] with aromatic substituents at 2 and 4 positions of the quinoline heterocycle. Some of these are annelated structures, thus we chose five basic structures with simple substituents in the corresponding positions in order to compare the values of the dihedral angles.[26–30] The values of the dihedral angles between the substituent and quinoline planes are 3.87(5)–26.7(1)° for position 2, and 52.27(5)–89.7(1)° for position 4 (Table 3).

In conclusion, we have developed a cascade reaction involving Friedländer/quinoxaline–benzimidazole rearrangement for the facile synthesis of 4-(benzimidazol-2-yl)quinoline and benzimidazolo[2,1-*a*]pyrrolo[3,4-*c*]quinoline derivatives. The mechanisms for the formation of the resulting 4-(benzimidazol-2-yl)quinoline and benzimidazolo[2,1-*a*]pyrrolo[3,4-*c*]quinoline derivatives are proposed to involve a new acid-catalyzed rearrangement of the



Scheme 3. A plausible mechanism for the formation of 4-(benzimidazol-2-yl)quinolines **5**.



Scheme 4. Reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-one (**1**) with ethyl acetoacetate (**6**).

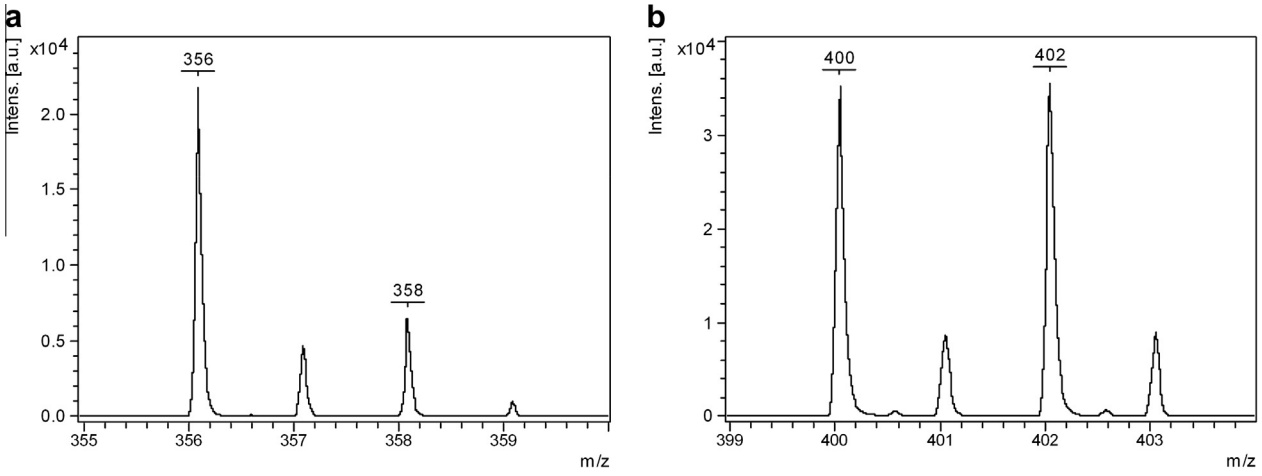


Figure 1. The characteristic molecular ion peaks for 4-(benzimidazol-2-yl)quinolines with the 4-chlorophenyl **5e** (a) and 4-bromophenyl **5b** (b) groups.

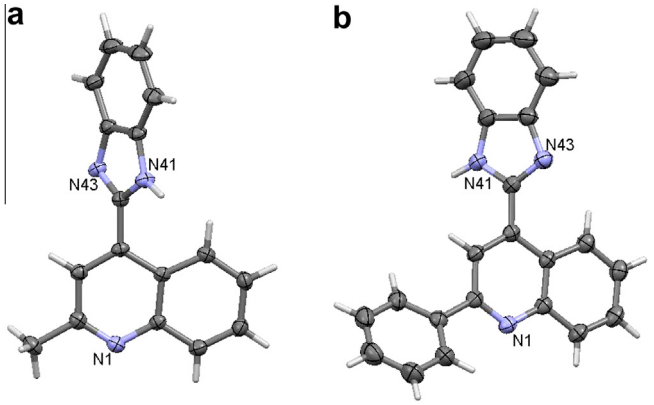


Figure 2. ORTEP plots of compounds **3** (a) and **5a** (b) and partial numbering schemes. Displacement ellipsoids are drawn at the 30% probability level. H-atoms are represented in stick mode for clarity. Solvent water molecules are omitted for clarity.

Table 3
The values of the dihedral angles between the quinoline system and the substituents at the 2 and 4 positions of the selected structures[26–30]

Substituent at position 2 of the quinoline heterocycle	Substituent at position 4 of the quinoline heterocycle	Quinoline heterocycle/ substituent 2	Quinoline heterocycle/ substituent 4	Ref.
Ph	Ph	21.3(1)	65.0(1)	25
Ph	Ph	23.05(7)	61.75(6)	26
2-Py	Ph	3.87(5)	52.27(5)	27
4-ClC_6H_4	4-$O_2NC_6H_4$	18.1(1)	64.8(1)	28
3-$MeOC_6H_4$	2-ClC_6H_4	26.7(1)	89.7(1)	29

spiro-quinoxalinones formed in situ from the reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones and ketones under modified Friedländer reaction conditions. This method has the advantages of mild conditions, simple work-up, high yields, and a wide substrate scope, which should make it very useful for the synthesis of multisubstituted and condensed quinolines.

Acknowledgments

This work was supported by the Russian Foundation for Basic Research (grants no 13-03-00123-a, 14-03-31194-mol_a).

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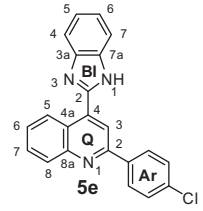
15. *Typical procedure for the synthesis of 2-aryl-4-(benzimidazol-2-yl)quinolines* ***5a–f***: 3-(2-Aminophenyl)quinoxalin-2(1*H*)-one (**1**) (0.20 g, 0.84 mmol) and acetophenone **4a–f** (2.36 mmol) in glacial AcOH (6 mL) were heated for 5 h at 55 °C. The solvent was evaporated and the residue was triturated with Et_2O (5 mL). The resulting precipitate was filtered off and dried under air to yield 9.00–14.40 mg (5–8%) of compound **2**. Purification by column chromatography with hexane/*i*-PrOH (98:2) as the eluent afforded analytically pure 7.20, 10.80 mg (4.0, 6.0%) of **2** as white crystals, R_f 0.58 ($CHCl_3$/*n*-C_6H_{14}/MeOH, 6:3:1), mp 299–300 °C (lit.[31] 294–295 °C). The ether filtrates were concentrated and the residues were purified by column chromatography with *i*-PrOH or a mixture of *n*-C_6H_{14}/*i*-PrOH as eluents to give analytically pure compounds **5a**,**c**,**d**,**e**. In the cases of acetophenones **4b** and **4f**, precipitation of crystals from the reaction mixture occurred, which were filtered off and washed with Et_2O (3 × 5 mL), and dried under air to afford analytically pure quinolines **5b** and **5f**. Additional amounts of quinolines **5b** and **5f** were obtained from the evaporated ether mother solution on triturating with *i*-PrOH (in the case of **5b**) and Et_2O (in the case of **5f**).



5e

Data for **5e**: lilac crystals, R_f = 0.60, *i*-PrOH. IR (Nujol, cm^{-1}) ν 3362, 3152, 3052, 1595, 1546, 1436, 1339, 1273, 1094, 837, 770, 745. ^1H NMR (400 MHz, DMSO-d_6) δ 7.29–7.37 (m, 2H, H5+H6 BI), 7.60 (d, 2H, J = 8.6 Hz, H3+H5 Ar), 7.68 (ddd, 1H, J = 7.7, 7.7, 1.4 Hz, H6 Q), 7.70–7.78 (m, 2H, H4+H7 BI), 7.84 (ddd, 1H, J = 7.6, 7.6, 1.6 Hz, H7 Q), 8.14 (d, 1H, J = 7.7 Hz, H8 Q), 8.30 (d, 2H, J = 8.6 Hz, H2+H6 Ar), 8.46 (s, 1H, H3 Q), 9.14 (dd, 1H, J = 7.7, 1.3 Hz, H5 Q), 13.36 (s, 1H, H1 BI); ^{13}C NMR (100 MHz, DMSO-d_6) δ 112.5 (C7 BI), 118.9 (C3 Q), 120.0 (C4 BI), 123.4 (C5 BI), 124.1 (C6 BI), 124.3 (C4a Q), 126.9 (C5 Q), 128.2 (C6 Q), 129.50 (C3+C5 Ar), 129.53 (C2+C6 Ar), 130.1 (C8 Q), 131.0 (C7 Q), 134.9 (C7a BI), 135.4 (C4 Ar), 136.4 (C4 Q), 137.5 (C1 Ar), 144.2 (C3a BI), 148.9 (C8a Q), 149.5 (C2 BI), 155.2 (C2 Q). MS (ESI) m/z 356 $[M+H]^+$; HRMS (MALDI) m/z $[M+H]^+$ calcd for $C_{22}H_{15}ClN_3$: 356.0949. Found: 356.0918. Calcd for $C_{22}H_{14}ClN_3$: C, 74.26; H, 3.97; N, 11.81. Found: C, 74.47; H, 3.86; N, 11.65.

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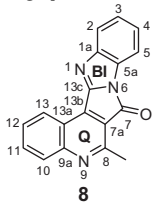
20. *Synthesis of 8-methyl-7H-benzimidazolo[2,1-a]pyrrolo[3,4-c]quinolin-7-one* (***8***). 3-(2-Aminophenyl)quinoxalin-2(1*H*)-one (**1**) (0.20 g, 0.84 mmol) and ethyl acetoacetate (**6**) (0.33 g, 2.53 mmol) in AcOH (6 mL) were heated for 6 h at 55 °C. The mixture was heated further for 3 h at reflux. After completion of the reaction, the solvent was evaporated and the residue was purified through a short pad of silica gel eluting with hexane/*i*-PrOH (96:4) to afford 0.18 g (75%) of analytically pure **8** as an orange powder.



8

Data for **8**: R_f 0.55, mp 216–218 °C. IR (KBr, cm^{-1}) ν 3422, 1753, 1618, 1561, 1483, 1429, 1365, 1290, 1129, 771, 748. ^1H NMR (DMSO-d_6, 400 MHz) δ 2.94 (s, 3H, CH_3), 7.24 (ddd, 1H, ^3J = 7.7, 7.4 Hz, ^4J = 1.1 Hz, H3), 7.33 (ddd, 1H, ^3J = 7.8, 7.6 Hz, ^4J = 1.1 Hz, H4), 7.60 (br dd, 1H, ^3J = 8.5, 7.8 Hz, H12), 7.69 (br d, 1H, ^3J = 7.7 Hz, H2), 7.70 (br d, 1H, ^3J = 7.7 Hz, H5), 7.79 (ddd, 1H, ^3J = 8.5, 7.8 Hz, ^4J = 1.2 Hz, H11), 7.97 (d, 1H, ^3J = 8.5 Hz, H10), 8.60 (d, 1H, ^3J = 8.5 Hz, H13); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz) δ 21.2 (CH_3), 112.1 (C5), 119.8 (C13a), 121.4 (C2), 123.8 (C7a), 124.8 (C3), 125.2 (C13), 127.2 (C4), 128.0 (C12), 128.7 (C10), 129.1 (C5a), 133.1 (C11), 138.9 (C13b), 149.2 (C1a), 150.8 (C9a), 154.6 (C13c), 155.8 (C8), 160.5 (C7); ^{15}N NMR (DMSO-d_6, 60 MHz) δ 316.1 (N9). MS (ESI) m/z 286 $[M+H]^+$, HRMS (MALDI) m/z $[M+H]^+$ Calcd for $C_{18}H_{12}N_3O$: 286.0975. Found: 286.0961. Calcd for $C_{18}H_{11}N_3O$: C, 75.78; H, 3.89; N, 14.73. Found: C, 75.53; H, 3.77; N, 14.55.

21. The X-ray diffraction data for crystals of **3** were collected on a Bruker AXS Smart APEX II CCD diffractometer at 296 K. *Crystallographic data for* ***3***. $C_{17}H_{13}N_3{\cdot}H_2O$, colorless prisms, formula weight 277.32, triclinic, $P\bar{1}$, a = 7.284(1) Å, b = 9.172(2) Å, c = 11.855(2) Å, α = 97.961(2)°, β = 100.902(2)°, γ = 111.339(2)°, V = 705.5(2) Å^3, Z = 2, ρ_{calc} = 1.305 g cm^{-3}, $\mu(\lambda MoK_\alpha)$ = 0.84 cm^{-1}, $F(000)$ = 292, reflections collected = 9000,

unique = 2771, $R_{(int)}$ = 0.0380, full matrix least squares on F^2, parameters = 203, restraints = 0. Final indices R_1 = 0.0528, wR_2 = 0.1190 for 1715 reflections with $I > 2\sigma(I)$; R_1 = 0.0979, wR_2 = 0.1426 for all data, goodness-of-fit on F^2 = 1.012, largest difference in peak and hole (0.310 and –0.165 e Å^{-3}).

22. The X-ray diffraction data for crystals of **5a** were collected on a Bruker AXS Smart APEX II CCD diffractometer at 296 K. *Crystallographic data for* ***5a***. $C_{22}H_{15}N_3{\cdot}H_2O$, colorless prisms, formula weight 339.39, monoclinic, $P2_1/c$, a = 13.514(3) Å, b = 10.286(2) Å, c = 13.488(3) Å, β = 105.677(3)°, V = 1805.0(6) Å^3, Z = 4, ρ_{calc} = 1.249 g cm^{-3}, $\mu(\lambda MoK_\alpha)$ = 0.79 cm^{-1}, $F(000)$ = 712, reflections collected = 13321, unique = 3543, $R_{(int)}$ = 0.0669, full matrix least squares on F^2, parameters = 247, restraints = 0. Final indices R_1 = 0.0540, wR_2 = 0.1183 for 1652 reflections with $I > 2\sigma(I)$; R_1 = 0.1430, wR_2 = 0.1566 for all data, goodness-of-fit on F^2 = 0.992, largest difference in peak and hole (0.188 and −0.174 e Å^{-3}).
23. Crystallographic data (except structure factors) for the compounds **3** and **5a** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 930952 and 930953, respectively. 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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