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# An efficient metal-free synthesis of 2-(pyrazin-2-yl)benzimidazoles from quinoxalinones and diaminomaleonitrile via a novel rearrangement

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ABSTRACT

A simple and highly efficient metal-free method for the synthesis of 2-(pyrazin-2-yl)benzimidazoles has been developed on the basis of the novel ring contraction of 3-aroyl- and 3-alkanoylquinoxalin-2-ones with diaminomaleonitrile.



Pyrazines are important flavor ingredients in food,[1] and have exhibited interesting anticancer[2] and antituberculosis[3] activities. They are reported to modulate the activity of CRF1 (corticotropin-releasing factor 1) receptors.[4] Besides, they are also versatile building blocks for the synthesis of VCAM-1 (vascular cell adhesion molecule-1) inhibitors,[5] pyrazine alkaloids (antineoplasmic activity),[2d] and imidazopyrazin coelenterazine (a bioluminescent agent).[6] Pyrazines are widely used as agrochemicals.[7] Due to their medicinal, agrochemical, and synthetic values, a number of methods have been developed for the synthesis of pyrazine derivatives, especially 2-(hetero)arylpyrazines. These include the cross-coupling of 2-chloropyrazine with: (a) ArMgX in the presence of $(PPh_3)_2PdCl_2/ZnCl_2$,[8] (b) $ArSnBu_3$ in the presence of $PdCl_2(PPh_3)_2/PPh_3$, (c) $Ar_4Sn$ (generated in situ from ArMgX and $SnCl_4$) in the presence of $Pd(PPh_3)_4$,[9] (d) $ArBF_3K$ in the presence of $PdCl_2$(dppf), (e) ArZnCl in the presence of $PdCl_2(PPh_3)_2$,[10] or (f) $ArB(OH)_2$ in the presence of $PdCl_2$(dppb)/$Na_2CO_3$.[11] 2-(Hetero)arylpyrazines can also be prepared via the couplings of vinyl triflate with 2-pyrazinylzinc bromide in the presence of $Pd(PPh_3)_4$, 2-pyrazinylthioether with $ArSnBu_3$ in the presence of $Pd(PPh_3)_4$/Cu(I)-3-methylsalicylate, or 2-pyrazinyl tributyltin with ArBr in the presence of $Pd(PPh_3)_4$, coupling of 2-chloropyrazine with heteroarenes in the presence of $AlCl_3$.[12] While these methodologies involve mild conditions, most of them, however, often require the use of expensive catalysts and reagents. Besides, the necessary organo-metallic reagents are in many cases either commercially unavailable or their preparation often involves cumbersome procedures.

Recently, we reported a new method for synthesizing 2-(benzimidazol-2-yl)quinoxalines by the reactions of aroyl(alkanoyl) quinoxalinones and 1,2-diaminobenzenes.[13a–c] The key step of this transformation involved a novel acid-catalyzed rearrangement of intermediate spiro-quinoxaline derivatives with contraction of the pyrazine ring of the quinoxalinone fragment. It was also shown that the scope of this rearrangement could be extended to the use of other functionalized quinoxalinones and N-nucleophiles for synthesizing various 2-(hetero)aryl-substituted benzimidazoles.[13d–f] Further exploration of this strategy has led to the development of a novel, inexpensive, simple, and scalable method for the synthesis of 2-(hetero)arylpyrazines. Here the results of our study on a novel rearrangement of 3-aroyl- and alkanoylquinoxalin-2(1*H*)-ones and 2,3-diaminomaleonitrile as a N-nucleophile under acid catalysis condition are presented.

To optimize the process, we initially carried out the reaction of 3-benzoylquinoxalin-2(1*H*)-one (**1a**) with 2,3-diaminomaleonitrile (**2**) in boiling acetic acid with various ratios of reagents and over different reaction times. Regardless of the molar ratio of the

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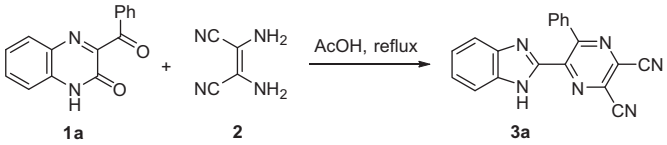
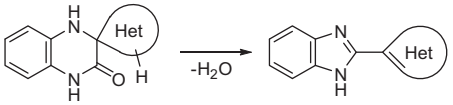



**Scheme 1.** Acid-catalyzed rearrangement.



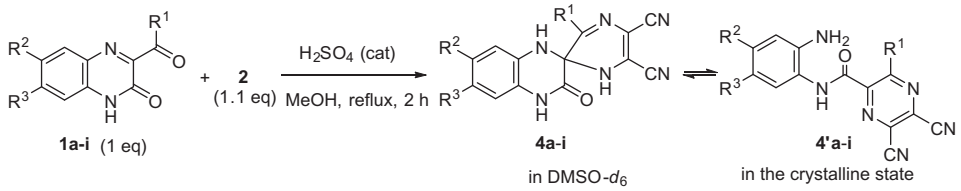

**Scheme 2.** A schematic presentation of the rearrangement.

reagents (1:1, 1:1.1, 1:2; **1a**:**2**) and reaction time (3, 9 or 17 h) the reaction proceeded in the same way with the formation of a ~45% yield of the rearrangement product **3a** (Scheme 1), whereas 50% of 3-benzoylquinoxalin-2(1*H*)-one (**1a**) was recovered. Diaminomaleonitrile **2** apparently undergoes polymerization. Adding a second equivalent of diaminomaleonitrile **2** to the reaction mixture obtained after boiling the equimolar ratio of reagents in acetic acid for 5 h did not lead to an increased yield of the desired product. Neither did heating for an additional 5 h.

In order to improve the yield of the rearrangement product we turned to our previously proposed hypothesis that 'any of the spiro derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one with at least one mobile hydrogen atom in their spiro-forming component are on their way to the benzimidazole derivative with the spiro-forming component in position 2' (Scheme 2).[14]

In accordance with this hypothesis there appeared the problem of the synthesis of the spiro[pyrazine-2,2′-quinoxaline]-3′(4′*H*)-one derivative. For this purpose we installed the necessary pyrazine ring system at position 2 of quinoxalin-2(1*H*)-one **1a** via the modified Kerner and Hinsberg[15] reaction (the synthesis of quinoxalines by the condensation of α-dicarbonyl compounds with 1, 2-diaminobenzene). This was achieved by the reaction of **1a** with diaminomaleonitrile **2** in a boiling solution of MeOH in the presence of a catalytic amount of $H_2SO_4$. In this reaction we considered 3-benzoylquinoxalin-2(1*H*)-one **1a** as a heteroanalogue of an α-dicarbonyl compound. The reaction proceeded smoothly for 2 h to give the desired spiro compound, 5,6-dicyano-3*R*-1*H*,1′*H*-spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-one (**4a**) in a 96% yield (Table 1,

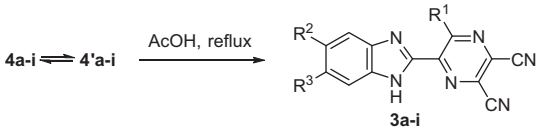
**Table 1**
Synthesis of 5,6-dicyano-3*R*-1*H*,1′*H*-spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-ones




| Entry | $R^1$ | $R^2$ | $R^3$ | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | Ph | H | H | **4a** | 96, 74[a], 91[b] |
| 2 | 4-$FC_6H_4$ | H | H | **4b** | 92, 85[a], 88[b] |
| 3 | 4-$ClC_6H_4$ | H | H | **4c** | 93, 82[a] |
| 4 | 4-$BrC_6H_4$ | H | H | **4d** | 93, 77[a] |
| 5 | 4-$IC_6H_4$ | H | H | **4e** | 95, 77[a] |
| 6 | Ph | H | COPh | **4f** | 95, 61[a] |
| 7 | Ph | H | $CO_2H$ | **4g** | 89, 64[a] |
| 8 | $CH_2Ph$ | H | H | **4h** | 95, 60[a] |
| 9 | Me | H | H | **4i** | 75, 61[a] |

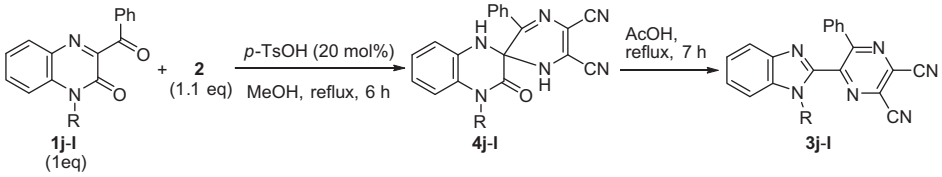
[a] *p*-TsOH was used instead of $H_2SO_4$.
[b] HCl was used instead of $H_2SO_4$.

**Table 2**
Acid-catalyzed rearrangement of 5,6-dicyano-3*R*-1*H*,1′*H*-spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-ones




| Entry | $R^1$ | $R^2$ | $R^3$ | Product | Time | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | Ph | H | H | **3a** | 10 min | 90 |
| 2 | 4-$FC_6H_4$ | H | H | **3b** | 10 min | 90 |
| 3 | 4-$ClC_6H_4$ | H | H | **3c** | 10 min | 91 |
| 4 | 4-$BrC_6H_4$ | H | H | **3d** | 10 min | 89 |
| 5 | 4-$IC_6H_4$ | H | H | **3e** | 10 min | 92 |
| 6 | Ph | H | COPh | **3f** | 3 h | 89 |
| 7 | Ph | H | $CO_2H$ | **3g** | 3 h | 85 |
| 8 | $CH_2Ph$ | H | H | **3h** | 10 min | 92 |
| 9 | Me | H | H | **3i** | 10 min | 93 |

**Table 3**
The synthesis of 4-alkyl 5,6-dicyano-1*H*,1′*H*-spiro[pyrazine-2,2′-quinoxalin]-3′-ones, and 1-alkyl-2-(pyrazin-2-yl)benzimidazoles




| Product | R | Yield[a] (%) | Product | R | Yield[a] (%) |
|---|---|---|---|---|---|
| **3j** | *n*-$C_4H_9$ | 95 | **4j** | *n*-$C_4H_9$ | 58 |
| **3k** | *n*-$C_8H_{17}$ | 94 | **4k** | *n*-$C_8H_{17}$ | 60 |
| **3l** | *n*-$C_9H_{19}$ | 97 | **4l** | *n*-$C_9H_{19}$ | 60 |

[a] Yield of purified product after filtration through a short silica gel plug with $CH_2Cl_2$ as eluent.

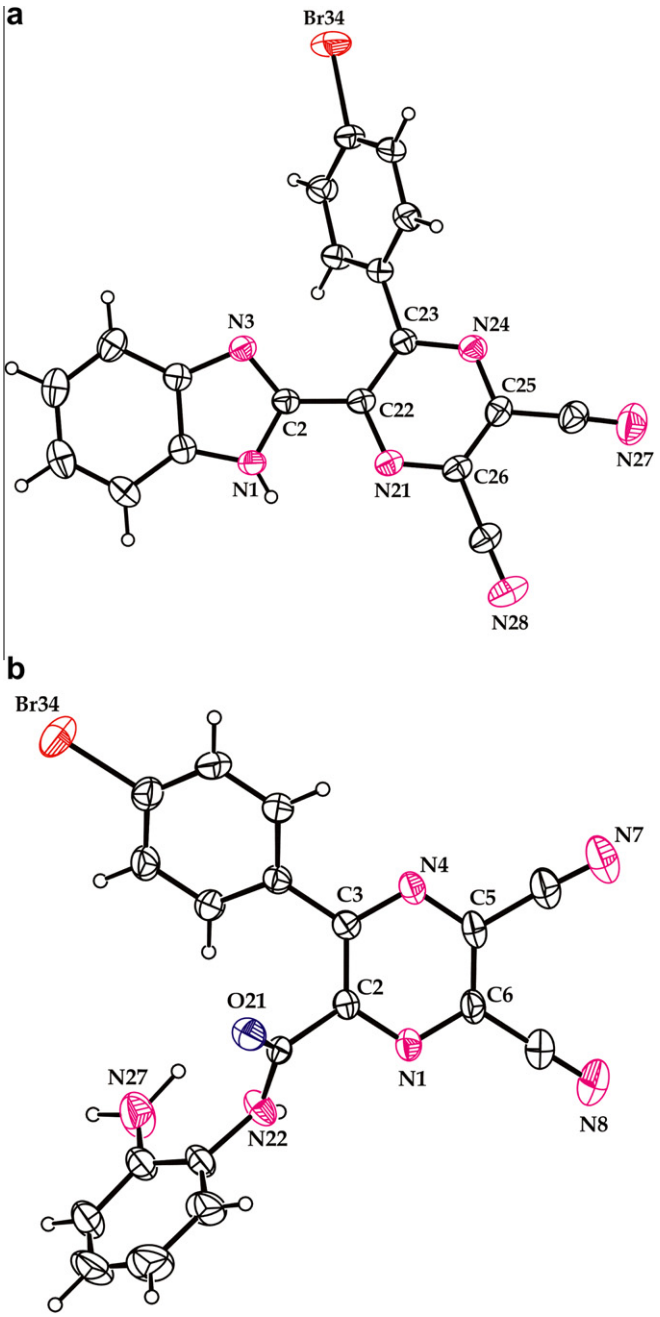



**Figure 1.** ORTEP plots of compounds **3d** (a) and **4′d** (b) and partial numbering schemes. Displacement ellipsoids are drawn at the 30% probability level. H-atoms are represented by spheres of arbitrary radii. The two acetic acid molecules in (a) are not shown.

entry 1). The optimum molar ratio of reagents **1a**:**2** was 1.0:1.1. Under these conditions other 3-aroyl- (**4a-g**) and 3-alkanoyl- (**4h**,**i**) derivatives of quinoxaline-2(1*H*)-ones behaved similarly resulting in high (75–96%) yields of the corresponding spiro-derivatives on reaction with diaminomaleonitrile **2** (Table 1). These examples of the reactions of **1a**,**d** with **2** showed that increasing the reaction time to 10 h resulted in a mixture of the products of rearrangement of **3a**,**d** and spiro-derivatives of quinoxalinones **4a**,**d** in a ratio of ~1:3 (yield 89%), and up to 20 h in a ratio of ~1:1 (yield 97%). When carrying out the reactions of quinoxalines **1a–i** with diaminomaleonitrile **2** for 6 h in the presence of *p*-TsOH (20 mol %) as catalyst the formation of spiro-compounds **4a–i** occurred in yields of 60–85% (Table 1). The reactions of quinoxalin-2(1*H*)-ones **1a**,**b** with **2** show that in the presence of catalytic amounts of HCl, spiro-compounds **4a**,**b** are formed in 2 h and the yields of the products were 91% and 88%, respectively (Table 1, entries 1 and 2).

Spiro-compounds **4a–e**,**h**,**i** without substituents on the benzene ring of the quinoxaline system were transformed quantitatively into the desired 2-(pyrazin-2-yl)benzimidazole **3a–e**,**h**,**i** in boiling AcOH in 10 min (Table 2, entries 1–5, 8 and 9). The substituted spiro-derivatives of quinoxalin-2(1*H*)-ones **4f**,**g** underwent the rearrangement only after 3 h in boiling AcOH (Table 2, entries 6 and 7).

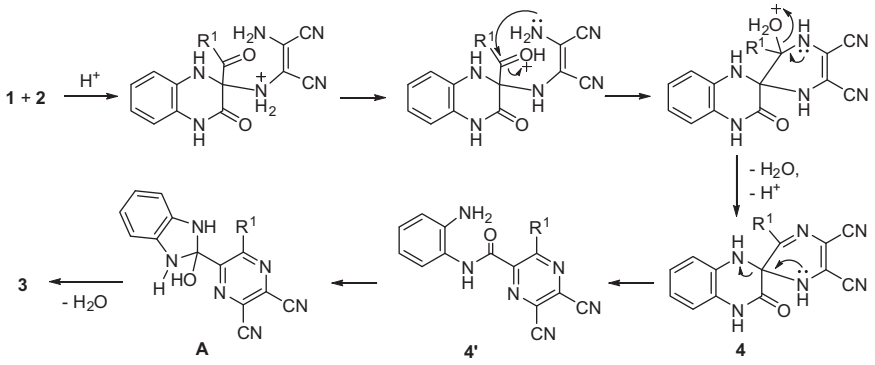
The formation of spiro-compounds also proceeded with N-alkylated derivatives of quinoxalin-2(1*H*)-ones **1j–l** to give N-alkylated spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-ones **4j–l** (Table 3). *p*-TsOH was more suitable as the catalyst for these cases. It should be pointed out that the rearrangement of N-alkylated spiro-compounds **4j–l** occurred more slowly than with nonalkylated spiro-compounds **4a–i**. Thus, heating spiro-compounds **4j–l** for 5 min resulted in formation of the product of rearrangement in a ~25% yield, 30 min: ~50%, 3 h: ~75%, 7 h: ~100%.[16,17]

The structures of compounds **3a–i**, **4a–i** and **4′a–i** were deduced from their elemental analyses and $^1$H and $^{13}$C NMR data.[16,17] The mass spectra of these compounds displayed molecular ion peaks at appropriate *m*/*z* values. The initial fragmentation of **3a–l** involved scission of the benzimidazole and pyrazine ring systems.[16,17]

The molecular structures of compounds **3d** and **4′d** were confirmed unambiguously by single-crystal X-ray analysis (Fig. 1a and b).[18–20]

It is worthy of note that the products of the reaction of 3-aroyl(alkanoyl)quinoxalin-2(1*H*)-ones **1a–i** and *N*-alkyl-3-benzoylquinoxalin-2(1*H*)-ones **1j–l** with diaminomaleonitrile **2** in DMSO-$d_6$ exist solely in spiro cyclic-forms **4a–l**, whereas in the crystalline state they exist only as open chain forms **4′a–l** (e.g., see Fig. 1b).

On the basis of the known chemistry of quinoxalinones,[21] and diaminomaleonitrile[22] and the above data, it is reasonable to assume that the formation of 2-(pyrazin-2-yl)benzimidazoles **3** involves addition of the amino group of diaminomaleonitrile **2** at the C(3) atom of quinoxalin-2(1*H*)-one **1** as the first step. The next step



**Scheme 3.** A plausible mechanism for the formation of 2-(pyrazin-2-yl)benzimidazoles **3**.

involves nucleophilic attack of the second amino group of **2** on the benzoyl carbonyl group to form the spiro-quinoxaline derivative **4**. Rearrangement of the spiroquinoxalinone **4** is then assumed to occur according to Scheme 3, which proceeds via a cascade involving: (a) acid catalysis ring-opening with cleavage of the C(3)-N(4) bond in the spiro-compound **4** with the formation of intermediate quinoxaline derivative **4′**, (b) intramolecular nucleophilic attack by the amino group on the carbonyl group with the formation of intermediate hydroxy-derivative **A**, and (c) the elimination of water leading to the final product **3** (Scheme 3).

To summarize, we have described an efficient and versatile metal-free method for the preparation of a series of 2-(pyrazin-2-yl)benzimidazoles. This was accomplished by the novel rearrangement of 3*R*-5,6-dicyano-1*H*,1′*H*-spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-ones easily obtained from 3-aroyl- and 3-alkanoylquinoxalin-2(1*H*)-ones on exposure to diaminomaleonitrile. The key advantages are the simplicity of the operation, high yields, easy availability of 3-aroyl-, and alkanoylquinoxalin-2(1*H*)-ones, as well as the simple work-up and purification of the products. 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.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.013.

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16. *Illustrative experimental procedure for the preparation of compounds* **3**. Method A. 2,3-Diaminomaleonitrile (**2**) (95 mg, 0.88 mmol) was added to a suspension of benzoylquinoxalin-2(1*H*)-one **1a** (0.2 g, 0.8 mmol) in AcOH (10 mL). The reaction mixture was heated at reflux with stirring for 3 h. The solvent was removed under reduced pressure and the residue treated with $H_2O$. The resulting precipitate was filtered, washed with $H_2O$ (20 mL) and dried in air to give a mixture of compounds **3a** and unreacted benzoylquinoxalin-2(1*H*)-one **1a** (0.23 g, 90%) in the ratio 1.5:1 (calculated from the $^1$H NMR spectrum). The mixture was recrystallized from AcOH/*i*-PrOH and the precipitate filtered to give analytically pure compound **3a** (0.11 g, 43%), mp 286–289 °C. [Found: C, 65.72; H, 3.70; N, 22.11. $C_{19}H_{10}N_6$·AcOH requires C, 65.97; H, 3.66; N, 21.99]; IR (KBr) $\nu_{max}$ = 1514, 1443, 1422, 1345, 1222, 765, 701 cm$^{-1}$; $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ = 7.26 (br s, 2H), 7.45 (dd, *J* = 7.4, 7.3 Hz, 2H), 7.51–7.56 (m, 2H), 7.54 (ddd, *J* = 7.2, 6.4, 1.1 Hz, 1H), 7.65 (dd, *J* = 7.8, 6.4 Hz, 2H), 12.96(s 1H). MS (EI), *m*/*z* [I(%)]: 323 (5), 322 (30) [M]$^+$, 321 (100), 320 (7), 218 (7). (The peaks of ions with relative intensity less then 5% are not specified).
*2-{3-(4-Bromophenyl)-5,6-dicyano[pyrazin-2-yl]}-benzimidazole* (**3d**): light brown powder; mp 300–303 °C. [Found: C, 56.81; H, 2.24; N, 21.07. $C_{19}H_9BrN_6$ requires C, 56.88; H, 2.26; N, 20.95]; IR (Nujol) $\nu_{max}$ = 3342, 1709, 1706, 1588, 1518, 1425, 1304, 1245, 1147, 1108, 1073, 1016, 935, 838, 802, 761 cm$^{-1}$; $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ = 7.25–7.29 (m, 2H), 7.55–7.59 (m, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 13.42 (br s 1H); MS (EI), *m*/*z* [I(%)]: 403 (5), 402 (29), 401 (100), 400 (30) [M]$^+$, 399 (95), 376 (8), 374 (8), 321 (10), 320 (19), 319 (18), 298 (1), 296 (11), 60 (11), 108 (15), 102 (9), 64 (5), 63 (7).
17. *Illustrative experimental procedure for the preparation of compounds* **4**. Method A. *p*-TsOH (28 mg, 0.16 mmol) was added to a suspension of benzoylquinoxalin-

2(1*H*)-one (**1a**) (0.2 g, 0.8 mmol) and 2,3-diaminomaleonitrile (**2**) (95 mg, 0.88 mmol) in MeOH (10 mL). The reaction mixture was heated at reflux with stirring for ca. 45 min until the formation of a homogeneous solution occured. After 10–15 min the precipitation of orange crystals occurred gradually and the reaction mixture was boiled for another 5 h. The mixture was cooled to room temperature and the precipitate filtered and dried in air to give 0.11 g (40%), of an analytically pure **4a**, mp 243–246 °C (dec). [Found: C, 66.97; H, 3.52; N, 24.78. $C_{19}H_{12}N_6O$ requires C, 67.05; H, 3.55; N, 24.69]; IR (Nujol) $\nu_{max}$ = 3443, 3366, 1650, 1628, 1557, 1459, 1378, 1302, 1254, 1217, 1151, 1077, 755 $cm^{-1}$; $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta$ = 6.77 (d, *J* = 7.8 Hz, 1H), 6.81 (ddd, *J* = 7.8, 7.6, 1.1 Hz, 1H), 6.95 (dd, *J* = 7.8, 6.4 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 7.30–7.43 (m, 3H), 7.70–7.73 (m, 2H), 7.98 (s, 1H), 10.44 (s, 1H), 11.25 (s, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-$d_6$) $\delta$ = 66.79, 105.07, 112.81, 114.90, 116.29, 116.79, 117.76, 120.19, 124.75 (br), 128.78, 129.15, 131.24, 136.70, 149.21, 161.38. MS (EI), *m*/*z* [I(%)]: 340 (11) $[M]^+$, 323 (9), 322 (27), 321 (100), 320 (8), 218 (8), 135 (19), 134 (5), 108 (5), 107 (22), 103 (7), 80 (14), 77 (5). (The peaks of ions with relative intensities less then 5% are not specified). The filtrate was evaporated in vacuo, the remaining solid was treated with $H_2O$ (20 mL) and the resulting precipitate filtered, dried in air and recrystallized from *i*-PrOH to give additionally 92 mg (34%) of compound **4a**.

18. The X-ray diffraction data for crystals of **3d** were collected on a Bruker AXS Smart APEX II CCD diffractometer at 296 K. *Crystallographic data for* **3d**. $C_{19}H_9Br_1N_6{\cdot}2C_2H_4O_2$, yellow needles, formula weight 521.34, triclinic, *P-1*, *a* = 8.639(2) Å, *b* = 11.695(2) Å, *c* = 12.595(3) Å, $\alpha$ = 84.919(2)°, $\beta$ = 88.871(2)°, $\gamma$ = 69.395(2)°, *V* = 1186.3(4) $Å^3$, *Z* = 2, $\rho_{calc}$ = 1.460 g $cm^{-3}$, $\mu(\lambda MoK_\alpha)$ = 17.74 $cm^{-1}$, F(000) = 528, reflections collected = 9075, unique = 4607, $R_{(int)}$ = 0.0225, full matrix least squares on $F^2$, parameters = 315, restraints = 0. Final indices $R_1$ = 0.0519, $wR_2$ = 0.1352 for 2964 reflections with $I > 2\sigma(I)$; $R_1$ = 0.0868, $wR_2$ = 0.1551 for all data, goodness-of-fit on $F^2$ = 1.021, largest difference in peak and hole (0.971 and –0.886 $eÅ^{-3}$).
19. The X-ray diffraction data for crystals of **4′d** were collected on a Bruker AXS Smart APEX II CCD diffractometer at 296 K. *Crystallographic data for* **4′d**. $C_{19}H_{11}Br_1N_6O_1$, yellow needles, formula weight 419.25, monoclinic, *P* $2_1/n$, *a* = 12.527(2) Å, *b* = 8.490(2) Å, *c* = 18.007(4) Å, $\beta$ = 105.125(2)°, *V* = 1848.8 (6) $Å^3$, *Z* = 4, $\rho_{calc}$ = 1.506 g $cm^{-3}$, $\mu(\lambda MoK_\alpha)$ = 22.45 $cm^{-1}$, F(000) = 840, reflections collected = 13578, unique = 3638, $R_{(int)}$ = 0.0873, full matrix least squares on $F^2$, parameters = 256, restraints = 0. Final indices $R_1$ = 0.0551, $wR_2$ = 0.1074 for 1645 reflections with $I > 2\sigma(I)$; $R_1$ = 0.1523, $wR_2$ = 0.1378 for all data, goodness-of-fit on $F^2$ = 1.003, largest difference in peak and hole (0.320 and –0.490 $eÅ^{-3}$).
20. Crystallographic data (excluding structure factors) for the structures reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 832661 and 832660 (compounds **3d** and **4′d**, respectively). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).
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