A Surprising Formation of Novel Bridged Bis-Benzimidazoles by Oxidation of Diaminoquinoxalines

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A synthesis of novel hexacyclic bis-benzimidazoles **6** starting from 2,3-diarylamino-quinoxalines *via* an oxidative cyclization cascade is described. These very stable and high-melting derivatives are featured by their strong fluorescence in the blue region of the visible spectrum. The cyclization reaction between 2,3-dichloroquinoxaline and 1,2-phenylenediamine did not lead to derivatives of type **6**. In this case, only fluoflavine **7** was isolated quantitatively.
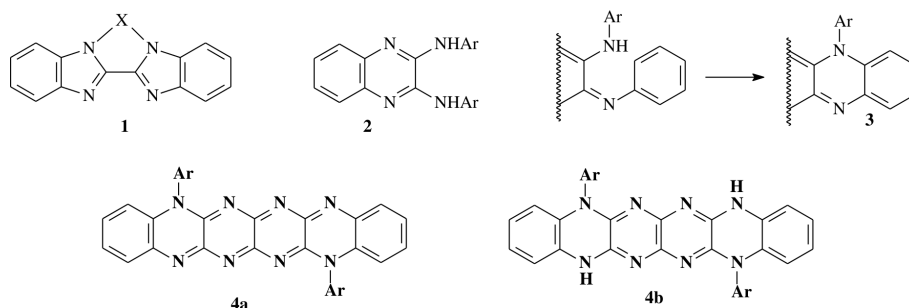
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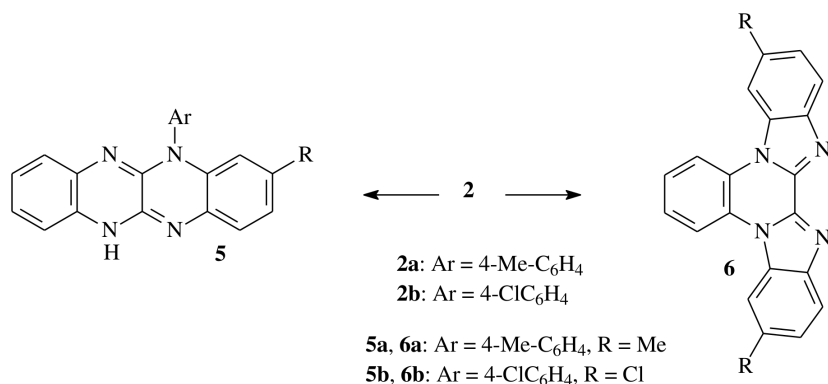
Introduction

2,2′-Bis-benzimidazoles (**1**) represent a well-established class of heterocycles and are of interest as ligands for the formation of functional metal complexes [1] as building blocks for supramolecular/polymeric architectures [2], for metal-organic frameworks [3], and as biologically active derivatives [4] (Scheme 1). In addition, bridged derivatives of bis-benzimidazole have often been applied in order to study the formation and dimerization of nucleophilic carbenes [5]. In 2009, Baldridge and Siegel reported the synthesis of a series of 1,1′-bridged 2,2′-bis-benzimidazoles for supramolecular applic-

ations [6]. Very recently, a Japanese patent described the use of bis-benzimidazo[1,2-*a*:2′,1′-*c*]quinoxalines **6** as electroluminescent materials [7].

Generally, bridged derivatives of type **1** have gained increased interest for the construction of supramolecular structures, as well as for functional metal complexes. Continuing our work focused on the oxidative *ortho*-annulation of vicinal amino-imino structural units [8], we were interested in the easily available 2,3-bis(arylamino)quinoxalines **2** [9]. Using optimized conditions, this methodology allows the simultaneous condensation of two ring systems to give ring-fused *N*-arylsubstituted quinoxalines **3** (Scheme 1). In principle, based on these facts a new synthetic strategy could

Scheme 1. General formulae for bridged 2,2′-bis-benzimidazoles **1** and 2,3-diarylamino-quinoxalines **2**; the oxidative *ortho*-annulation approach to give ring-fused quinoxalines **3** and derivatives of octaaza-hexacenes **4a**, **b**.

2a: Ar = 4-Me-C$_6$H$_4$
2b: Ar = 4-ClC$_6$H$_4$

5a, **6a**: Ar = 4-Me-C$_6$H$_4$, R = Me
5b, **6b**: Ar = 4-ClC$_6$H$_4$, R = Cl

Scheme 2. Two possible products of oxidative annulation of 2,3-bis(arylamino)quinoxalines **2**: fluoflavines **5** and hexacyclic 2,2-bis-(benzimidazoles) **6**.

be developed for oligoaza-acenes which are important building blocks for organic electronics. This has been successfully implemented in the past for derivatives of octaaza-hexacene **4a** and their leuco-forms **4b** [10] (Scheme 1), however with other mechanistic interpretations.

Results and Discussion

Based on our previous work we employed the oxidative *ortho*-annulation method for the syntheses of new types of aza-acenes. Several oxidizing reagents combined with potassium/sodium carbonate (the addition of a base resulted in shorter reaction times and higher yields) have been previously employed. In these experiments, the combination of bis(trifluoroacetoxy)iodbenzene and sodium carbonate (substrate : oxidizing reagent = 1 : 1.2 – 1.5) proved to be the best for the transformation of quinoxalines of type **2**. Upon completion of the reaction, TLC indicated that the resulting mixture consisted of a broad spectrum of highly fluorescent compounds. We succeeded in isolating one product, which was exhibited by a strong blue fluorescence, by employing fractional precipitation/recrystallization. The product was well soluble in hot DMSO and pyridine and formed yellow solutions; its solubility in other common solvents was rather low. All attempts to isolate by-products and/or intermediates were fruitless; the mass spectra only indicated substances with low molecular mass, most likely resulting from oxidative degradation processes.

Based on previous experimental findings, tetracyclic compounds of type **5** (Scheme 2) were expected. However, the first indications for the formation of new and unexpected products were provided by the NMR spectra. Thus, the ^{1}H NMR spectrum of the oxidation product from **2a** revealed a symmetric structure. In addition
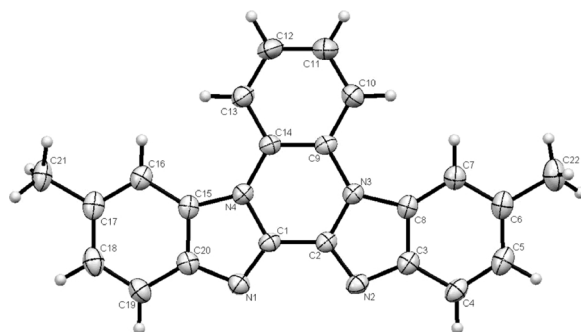

Fig. 1. Molecular structure of bis-benzimidazole **6a** in the crystal (displacement ellipsoids at the 50 % probability level, H atoms as spheres with arbitrary radii).

to the characteristic signals for aryl protons only one methyl group was detected at δ = 2.64 ppm, and no signal for NH was present. A single-crystal X-ray analysis allowed the unambiguous structural assignment of these compounds, as shown in Fig. 1. Hence, the cyclization products **6** have the structure of bis-benzimidazo[1,2-*a*:2′,1′-*c*]quinoxaline.

As depicted in Fig. 1, the hexacyclic compound **6a** has approximate C_{2V} symmetry in the solid state. The C_{2V} symmetry is weakly distorted in the crystal state as evidenced by the non-zero value of the dihedral angle N1–C1–C2–N2. Furthermore, pyridine is incorporated as a solvent molecule in the crystal structure of **6a**. The comparison with the planar molecular structure of 2,2′-bis(benzimidazole) [11] revealed that the central bond C1–C2 in **6a** is slightly shortened (143.0(4) *vs.* 143.5(5) pm). Due to the *o*-phenylene bridging of the nitrogen atoms N3 and N4, the angle between N1–C1–C2 in **6a** is expanded to 126.7(3)° compared to 122(1)° in 2,2′-bis(benzimidazole). The bonds N1–C1 and N2–C2 (130.4(4) pm), respectively, have clearly a double bond character. It is noteworthy
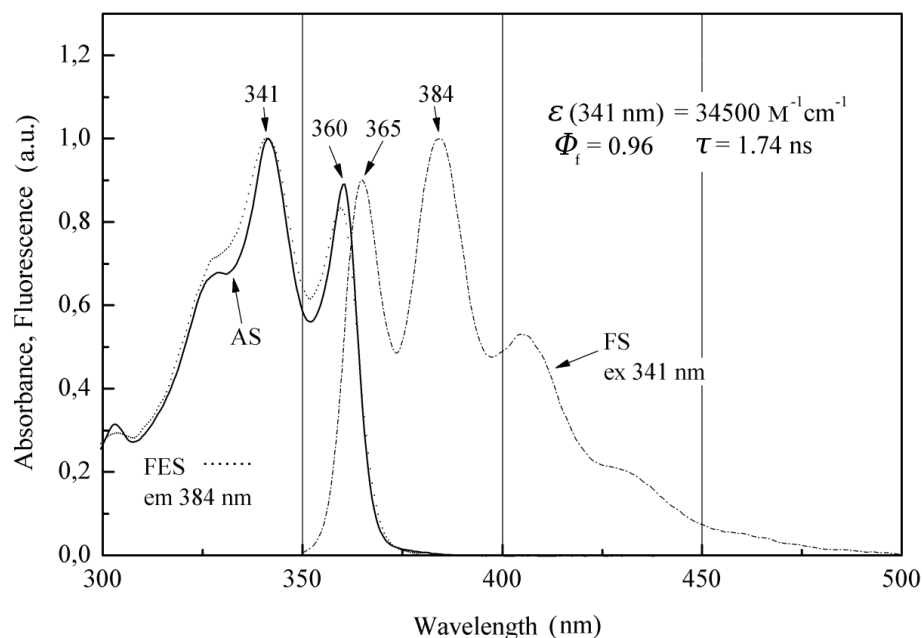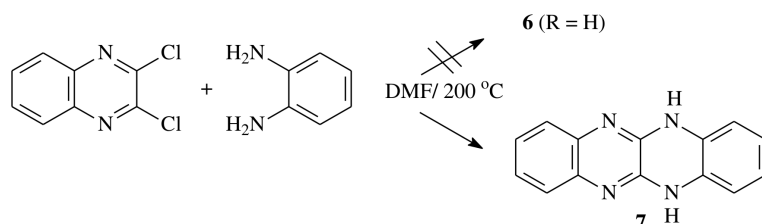
Fig. 2. Normalized absorption, fluorescence excitation (measured at 384 nm) and fluorescence emission (excitation at 341 nm) spectra of compound **6a** measured in dioxane.

Scheme 3. The cyclization reaction of 2,3-dichloroquinoxaline with *o*-phenylenediamine to give fluoflavine **7**.

that the strong blue fluorescence of **6a** in solution at $\lambda = 384$ nm has a quantum yield of close to 100 % and a fluorescence lifetime of 1.74 ns (Fig. 2). The small Stokes shift and the mirror symmetry indicate only small differences in the geometry between the ground and the first excited electronic states. A quantum yield of 60 % was determined for compound **6b**. Additionally, due to their 1,4-diazadiene subunit, derivatives **6** possess good prerequisites for the complexation of catalytically active metals. For instance, new ruthenium complexes were synthesized which show some unusual spectral properties. These results will be the object of a separate publication. The features reported above make the new bis-benzimidazoles **6** interesting for the purpose of application as a sensor, label and scintillation counter.

From a literature search for the molecular structure of **6a**, a note was found on the synthesis of a structurally homologous derivative [12]. Thus, the synthesis is described starting from 2,3-dichloroquinoxaline

and 1,2-phenylenediamine, however, its structure assignment was only based on elemental analysis and IR and MS data.

Furthermore, we were unsuccessful in the synthesis of **6** using this protocol. In all attempts, only 5,12-dihydrochinoxalino[2,3-*b*]quinoxaline "fluoflavine" (**7**) was isolated (Scheme 3), whereby the mass spectra of its dihydrochloride showed the same isotopic peaks as bis-benzimidazo[1,2-*a*:2′,1′-*c*]quinoxaline **6** (R = H). Derivative **7** was further characterized by its NMR and MS data. To our knowledge, therefore, the described fluoflavines **7** are the result of the reaction reported in lit. [12], and the bis-benzimidazoles of type **6** were formed in trace amounts at best, and failed to experimentally verify the typical fluorescence of **6** in this case.

We postulate the following mechanism (Scheme 4) for the formation of the bis-benzimidazo[1,2-*a*:2′,1′-*c*]quinoxalines **6**. Firstly, the oxidation takes place with the intermediate formation of the radical cation **[2′]**$^{\cdot+}$
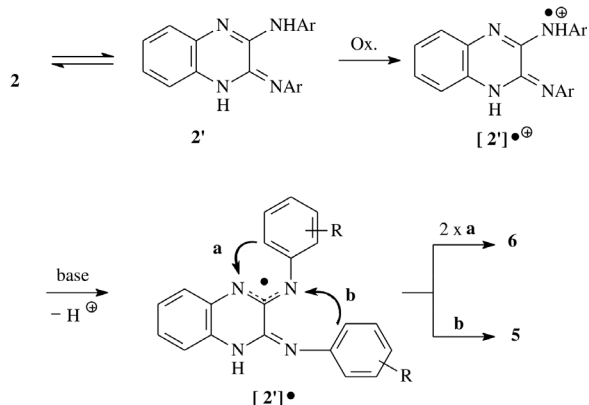
Scheme 4. Mechanistic interpretation of the formation of derivatives of type **6**.

derived from a secondary amine. A relatively strong acidity has been predicted for these radical cations and, consequently, deprotonation may result in the aminyl radical **[2′]**. The latter can be regarded as a delocalized 1,3-diazaallyl radical, which is able to attack intramolecularly two different aromatic rings. According to **Way a**, the angular annulation under formation of a ring-fused imidazole takes place; the same oxidation-cyclization sequence including the second amidine substructure finally leads to the isolated products of type **6**. One the other hand, the attack of the aromatic ring of the second amidine (**Way b**) should be possible, thus forming ring-fused pyrazine systems of type **5**. Although different, highly fluorescent products were detected by TLC, and it was not possible to isolate the substituted fluoflavines. With a view to the cyclization reaction calculations using the recently developed B2PLYP-D hybrid functional, with the def2-TZVP-basis set, and the B3LYP/6-311+G(d,p) geometries for the energy determinations [8a] clearly favor the radical mechanism, which shows the lowest activation barrier.

Conclusions

In summary, we report a new formation reaction of highly fluorescent, hexacyclic bis-benzimidazoles of type **6**. These highly symmetric heterocycles are not only new examples for bis-benzimidazoles but also interesting 1,4-diazadienes, capable of forming metal complexes. Evaluation of the scope of this ring-fusion method, as well as the inclusion of groups for subsequent coupling reactions, are the subject of current research and will be reported in due course.

Experimental Section

Unless otherwise indicated, all reagents were purchased from commercial suppliers and were used as received. Starting materials that were not commercially available were prepared according to literature procedures, cited in the text. Reactions were monitored by TLC using SiO_2 (silica gel 60 F254) from Fluka. Melting points were measured with a digital detector system KSPS 1000 from Krüss and are uncorrected. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC 250 (250/60 MHz) or Bruker DRC-400 (400/100 MHz) spectrometer, using residual solvent peaks as internal standards. Mass spectra were measured with a Finnigan MAT SSQ 710 Fison Trio 200 (EI) instrument. Elemental analyses were carried out with an automatic analyzer LECO, CHNS-932. The UV spectra were measured with an UNICAM UV500 spectrometer from Thermo Electron Corporation. For IR spectra a BIO-RAD FTS-25 instrument was used. Absorption spectra were recorded on a LAMBDA 16 spectrophotometer (Perkin Elmer). Fluorescence emission and excitation spectra were measured using a LS50B luminescence spectrometer (Perkin Elmer). Fluorescence quantum yields were calculated relative to quinine sulfate (purum; Fluka) in 0.1 N H_2SO_4 used as a standard ($\phi_f = 0.55$). The absorbance at the excitation wavelength was kept below 0.05 for the samples and the reference. The fluorescence lifetime was determined with a CD900 time correlating single photon counting spectrometer (Edinburgh Instruments).

4,4′-Dimethyl-bis-benzimidazo[1,2-a:2′,1′-c]quinoxaline (6a)

In a stirred suspension of sodium carbonate (1.56 g, 14.7 mmol) in trichloromethane (150 mL), 2,3-bis(4-tolyl-amino)quinoxaline (**2a**) (0.5 g, 1.47 mmol) was dissolved. To this mixture bis(trifluoroacetoxy)iodobenzene (3.0 g, 6.97 mmol) was added within 3 min. The progress of the oxidation reaction was monitored by irradiation of the reaction mixture with UV light (350 nm). Immediately after the reaction mixture developed a deep blue fluorescence, isopropyl alcohol (100 mL) was added, and the reaction mixture was stirred for 5 additional minutes. Subsequently, the solvent was removed *in vacuo*. To the resulting dark-red solution, sodium carbonate was added until the development of gases ceased. The mixture was filtered off and after removing the isopropyl alcohol, the red filtrate was concentrated to dryness under fine vacuum conditions. Dissolving the red residue in ethyl acetate (20 mL) under warming resulted in a colorless precipitate overnight. The precipitate was filtered off and washed with ethyl acetate. Recrystallization from pyridine yielded colorless crystals of **6a** (53 mg, 11 % yield); M. p. 320 °C (decomp.). – IR (KBr) (intensity): v (cm^{-1}) = 3311 (w), 3181 (w), 3064 (w), 3020 (w), 2909

(w), 1638 (m), 1597 (m), 1560 (m), 1499 (s), 1485 (s), 1447 (m), 1378 (s), 1330 (s), 1290 (s), 1284 (m), 1216 (m). – UV (DMSO): λ_{max} (lg ε) = 306 (3.9), 331 (4.4), 344 (4.5), 364 (4.5). – Emission (dioxane), (%): 365 nm (85), 385 (100), 405 (60). – Fluorescence quantum yield (ϕ_A): 0.96; fluorescence lifetime: 1.74 ns. – MS (EI): m/z (%) = 336 (85), 333 (8), 306 (2), 283 (2), 257 (2), 232 (2), 204 (12), 167 (30), 147 (8), 116 (3), 97 (10), 77 (12), 69 (65), 50 (20), 44 (100). – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.64 (s, 12H), 7.34 (d, J = 8.4 Hz, 2H), 7.68 – 7.71 (m, 2H), 7.89 (d, J = 8.4 Hz, 2H), 8.47 (s, 2H), 8.79 – 8.82 (m, 2H). – ^{13}C NMR (22.5 MHz, [D$_6$]DMSO): δ = 22.0, 114.4, 117.3, 120.7, 126.2, 126.3, 126.6, 131.7, 135.1, 143. – C$_{22}$H$_{16}$N$_4$ (336.40): calcd. C 78.55, H 4.79, N 16.66; found C 78.74, H 4.70, N 16.51.

4,4′-Dichloro-bis-benzimidazo[1,2-a:2′,1′-c]quinoxaline (6b)

Compound **6b** was obtained by the same procedure by using 2,3-bis(4-chlorophenylamino)quinoxaline **2b** as starting material as colorless crystals (Yield 13 %); M. p. 350 °C (decomp.). – IR (KBr) (intensity): ν (cm^{-1}) = 3462 (m), 3128 (w), 3081 (w), 1782 (w), 1639 (m), 1596 (m), 1563 (m), 1497 (s), 1478 (s), 1435 (s), 1377 (s), 1327 (m), 1288 (m). – UV (DMSO): λ_{max} (lg ε) = 307 (3.5), 328 (3.9), 344 (4.1), 363 (4.1) nm. – Emission (dioxane) (%): 389 nm (100), 410 (60). – MS (FAB in nba): m/z (%) = 379 (15), 377 (18), 364 (3), 329 (10), 290 (30), 258 (20), 242 (22), 226 (20), 212 (15). – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.61 (d, J = 8.6 Hz, 2H), 7.67 – 7.71 (m, 2H), 8.03 (d, J = 8.6 Hz, 2H), 8.78 – 8.81 (m, 4H). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 114.7, 117.7, 122.5, 125.8, 126, 127, 130.1, 132.1, 140.7, 143.8. – C$_{20}$H$_{10}$Cl$_2$N$_4$ (377.23): calcd. C 63.68, H 2.67, N 14.85, Cl 18.80; found C 63.56, H 2.70, N 14.71, Cl 18.89.

5,12-Dihydroquinoxalino[2,3-b]quinoxaline, "fluoflavine" (7)

2,3-dichloroquinoxaline (2.0 g, 10 mmol) and 1,2-phenylenediamine (2.17 g, 20 mmol) were dissolved in dry dimethylformamide (200 mL). The colorless solution was heated under reflux to 200 °C whereby at 50 °C the color of the solution turned to red. After the temperature reached 165 °C, a yellow-orange precipitate was formed. After 1 h reaction time, the mixture was cooled to r. t. and was poured into crushed ice. The slurry was filtered off, and the precipitate was dried. Recrystallization from methanol resulted in a yellow amorphous powder. (Yield 2.35 g, 10 mmol, 100 %). – ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 6.57 (m, 4H), 7.01 (m, 4H), 9.91 (s, 2H). – MS (EI): m/z (%) = 234 (100), 233 (39), 206 (5), 192 (2), 179 (2), 129 (1), 117 (8), 102 (4), 76 (1), 51 (1), 28 (4). – C$_{14}$H$_{10}$N$_4$ (234.26): calcd. C 71.28, H 4.30, N 23.92; found C 71.37, H 4.22, N 24.05.

Crystal structure determination

The intensity data of **6a** were collected on a Nonius KappaCCD diffractometer using graphite-monochromatized MoK_α radiation. Data were corrected for Lorentz and polarization effects but not for absorption [13, 14]. The structure was solved by Direct Methods (SHELXS-97 [15]) and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97 [15]). All hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically. The software XP (Siemens Analytical X-ray Instruments, Inc.) was used for structure representations.

Crystal structure data for **6a**: C$_{22}$H$_{16}$N$_4$, 2 (C$_5$H$_5$N), M_r = 494.59, colorless prism, size 0.04 × 0.04 × 0.03 mm^3, triclinic, space group $P\bar{1}$, a = 10.2821(9), b = 11.5712(9), c = 11.8386(9) Å, α = 78.252(5), β = 79.965(4), γ = 65.744(4)°, V = 1250.77(17) Å^3, T = −140 °C, Z = 2, $\rho_{calcd.}$ = 1.31 g cm^{-3}, μ (MoK_α) = 2.9 cm^{-1}, $F(000)$ = 520 e, 8918 reflections in h (−11/13), k (−14/15), l (±15), measured in the range 1.95° ≤ θ ≤ 27.50°, completeness 98.6 %, 5678 independent reflections, R_{int} = 0.0364, 3164 reflections with F_o ≥ 4σ(F_o), 345 refined parameters, 0 restraints, $R1_{obs}$ = 0.0907, $wR2_{obs}$ = 0.2289, $R1_{all}$ = 0.1597, $wR2_{all}$ = 0.2766, GOOF = 1.032, largest difference peak / hole: 0.493 / −0.434 e Å^{-3}.

CCDC 809050 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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