Nucleophilic Substitution of 4*H*-Imidazoles – A Key Step in the Synthesis of Fused Imidazoles and New Chromophores

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Dedicated to Professor Dirk Walther, Jena, on the occasion of his 60th birthday

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The electrophilic properties of the 4*H*-imidazoles **1** and their protonated derivatives **2** permit the introduction of nucleophilic building blocks, as illustrated by reactions of **1** with selected amines. Depending on the nature of the amine and the substituents R^1 on the heterocycle **1**, single (**3**) or double (**4**) transamination is observed. The ^{1}H-NMR spectra of the products, as well as X-ray structure analyses of compounds **3f** and **4c**, confirm that the residues at the 4- and/or 5-positions of **1** are exchanged. The tautomerism between **3e–h** and **3e′-h′** seems to be central to the chemistry of these mixed substituted derivatives. Using orthoesters and acetophenone dimethylacetal as cyclization partners, the imidazo[4,5-*d*]imidazoles **5** and the 4*H*-imidazo[4,5-*b*]pyrazines **6** are obtained, respectively. Reduction of **3e** with Zn/HCl or H_2S leads to the air-sensitive, strongly fluorescent leuco compounds **8**. Quenching of **8** by addition of aromatic aldehydes results in a condensation reaction and, coupled with the subsequent redox disproportionation, this conversion constitutes an alternative route to imidazo[4,5-*d*]imidazoles of type **11**. The unexpected reaction of **3e–h** with Lawesson's reagent allows synthesis of the 6-azapentafulvenes **14**. The relevant spectral data show **14** to be members of a new chromophoric system, in which an electron-rich five-membered ring is coupled with an electron-deficient ring.

Introduction

The bathochromic shift of about 150 nm observed upon protonation of the recently described derivatives of 4*H*-imidazoles **1**[1] can be attributed to transformation of the cyclic *mero*-polymethine-type chromophore into the polymethinic π-bond system of the iminium salt **2**. On the basis of the donor–acceptor concept devised by Gompper et al.,[2] the resulting cation can also be regarded as an anti-aromatic 1,3-diazacyclopentadienylium salt **2′**. Application of NICS (nucleus independent chemical shift) calculations, as described by Schleyer et al.,[3] as a classification scheme of cyclic conjugated systems on the basis of their magnetic properties, led to Fabian's[4] prediction of weak anti-aromatic bonding character ($\delta = +4.8$) for **1**. A larger NICS factor of $\delta = +7.8$ was calculated for protonated **2**, indicating at least an involvement of the $4n(\pi)$ system **2′**. Considering the π electrons of the amino residues, an extension of delocalization is possible. The resonance structure **2′′** thus seems to be favoured for the bonding state in such heterocyclic systems.

In any case, protonation of **1** should be accompanied by an increase in the electrophilic character of the ring carbon atoms, especially at the 4- and 5-positions of the heterocycle. By analogy with well-known substitution reactions of iminium salts, the delocalization of a positive charge in systems of type **2** could possibly be expected to allow the introduction of nucleophilic building blocks. Such nucleophilic substitutions have previously been described for donor–acceptor substituted cyclopentadienylium salts[5] and their corresponding heterocyclic systems.[6] This stimulated us to investigate whether or not the 4*H*-imidazoles **1** or their protonated forms **2** are able to undergo substitution reactions with nucleophiles.

Results and Discussion

In order to experimentally evaluate the aforementioned possibility, we reacted **1** with various substituted anilines (Scheme 1). In most cases, that a substitution reaction had indeed occurred was evident from a rapid color change. Addition of a catalytic amount of acid, thereby generating the protonated heterocycle **2**, led to a shortening of the reaction times, but was found not to be essential for the substitution reaction. The aromatic residue R^1 in the 4- and 5-positions could, in principle, be singly (**3**) or doubly (**4**) exchanged. As a consequence, an equilibrium between **3** and **4** was observed in the course of the substitution reaction. The position of this equilibrium was seen to be strongly influenced by the nature of the amine as well as by the substituents R^1 at the heterocycle **1**. For example, both tolyl residues are replaced in near quantitative yield when **1a** is reacted with donor-substituted aromatic amines such as anisidine or 4-dimethylaminoaniline to form the derivatives **4a** and **4b**. Because of the higher yield obtained in this reaction as compared to a previously described synthesis,[1] this twofold

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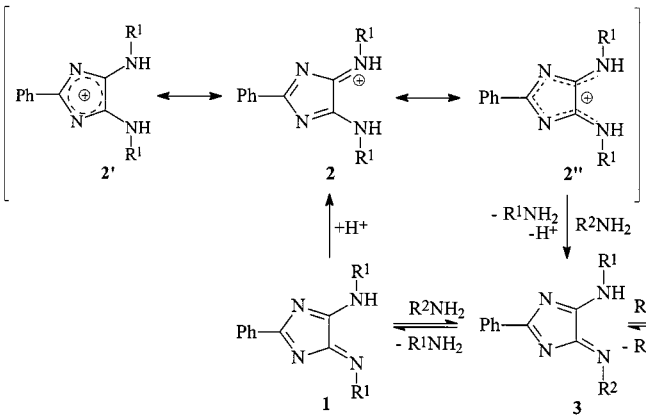


1,2	R^1
a	4-CH_3-C_6H_4
b	4-CH_3O-C_6H_4
c	4-$(CH_3)_2N$-C_6H_4
d	4-$(CH_3)_3C$-C_6H_4

3	R^1	R^2
a	4-CH_3-C_6H_4	4-CH_3O-C_6H_4
b	4-CH_3-C_6H_4	4-$(CH_3)_2N$-C_6H_4
c	4-CH_3-C_6H_4	CH_3
d	4-CH_3-C_6H_4	C_2H_5
e	4-CH_3-C_6H_4	H
f	C_6H_5 (^{15}N-labelled aniline)	H
g	4-$(CH_3)_3C$-C_6H_4	H
h	4-CH_3O-C_6H_4	H
i	4-CH_3-C_6H_4	$N(CH_3)_2$

4	R^2
a	4-CH_3O-C_6H_4
b	4-$(CH_3)_2N$-C_6H_4
c	CH_3
d	C_2H_5

Scheme 1

transamination is the method of choice for the synthesis of the deep-blue compound **4b**.

In contrast, only single transamination was observed for the 4*H*-imidazoles **1b** and **1c**. Thus, treatment of **1b** and **1c** with *p*-toluidine resulted in the unsymmetrically substituted derivatives **3a** and **3b** as the main products. As is evident from the ^{1}H-NMR spectra of compounds **3**, the specific nature of the substituents in the 4- and 5-positions leads to a suppression of the strong intermolecular proton-transfer that is usually a characteristic feature of solutions of 4*H*-imidazoles of type **1**.[1] For example, the signal due to the exocyclic NH proton was detected at $\delta = 5.26$ in the ^{1}H-NMR spectrum of **3a**.

Aliphatic 4*H*-imidazoles have not previously been obtained through cycloacylation reactions with benzamidine owing to the low stability of aliphatic bis(imidoyl) chlorides of oxalic acid.[7] Moreover, the aminolysis of 2,4,5-trichloro-2-phenyl-2*H*-imidazole[8] is, as far as we are aware, a non-selective reaction that often leads to mixtures of products. In contrast to these known procedures, **1a** reacts almost quantitatively with solutions of methyl- or ethylamine to form the desired bis(alkyl)-substituted 4*H*-imidazoles **4c** and **4d**. Unfortunately, distillation resulted in removal of the aliphatic amines, which led to a retro reaction with toluidine. As a consequence, the corresponding unsymmetrical derivatives **3c** and **3d** could be detected by TLC and characterized by MS.

The methyl derivative **4c**, having a less extended π-system, shows an absorption at $\lambda_{max} = 403$ nm (*cf.* **1a**: $\lambda_{max} = 483$ nm) in its UV/vis spectrum. A remarkable yellowish fluorescence is also observed for solutions of **4c**. Single-crystal X-ray analysis allowed an unambiguous structural

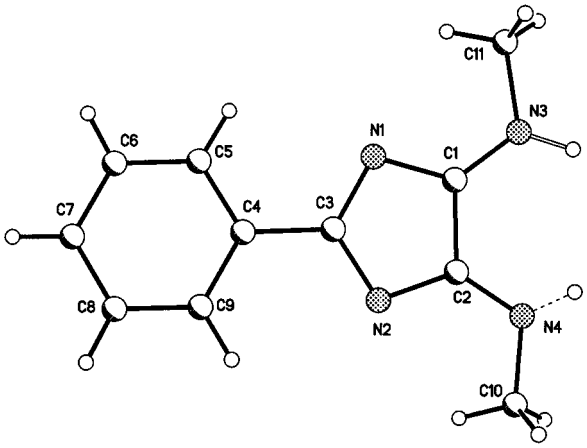


Figure 1. X-ray structure of **4c**; the numbering corresponds to that used for the X-ray analysis; selected distances [Å] and angles [°]: C1–N1 1.378(2), C3–N1 1.351(2), N2–C3 1.375(2), N2–C2 1.358(2), C1–C2 1.508(2), C1–N3 1.297(2), C2–N4 1.308(2); N1–C1–N3 127.4(1), N2–C2–N4 126.7(1), N1–C3–N2 118.7(1), N2–C2–C1 108.3(1), N1–C1–C2 107.3(1)

assignment of this compound, as shown in Figure 1. The structural details found for **4c** are very similar to those reported for the bis(aryl)-substituted 4*H*-imidazole **1a**.[1] For example, **1** and **4c** have very similar C–N bond lengths in their heterocyclic moieties (1.35 to 1.37 Å). In keeping with the crystal structure of **1a**, the C1–C2 bond length in **4c** [1.508(2) Å] is considerably longer than typical C_{sp2}–C_{sp2} bonds found in conjugated systems.[9]

Due to the possibility of carrying out further synthetic transformations, the synthesis of 5-amino-4*H*-imidazol-4-imine was of special interest. Treatment of **1a** with aqueous ammonia, however, resulted only in one transamination,

after which the aryl-substituted 4*H*-imidazoles **3e–h** could be isolated in good yields. Twofold substitution could not be realized by varying the reaction conditions (solvent, temperature, and/or addition of acids), nor by using excess gaseous ammonia.

The X-ray crystal structure of compound **3f**, which is representative of these unsymmetrically substituted 4*H*-imidazoles, is illustrated in Figure 2. Both NH protons are seen to be bound to a single nitrogen atom. Pronounced intra- and intermolecular hydrogen bonds lead to the formation of discrete dimeric subunits showing an essentially in-plane arrangement of the two imidazole substructures. Two distinct broad singlets due to the NH protons are observed at $\delta = 8.90$ and 8.57 in the ^{1}H-NMR spectrum of **3f** at –60 °C. A fixed tautomeric form at the aryl nitrogen could be excluded by NOESY experiments. Instead, the observed intramolecular cross-peaks indicate that there is hindered rotation about the C3–N3 bond.

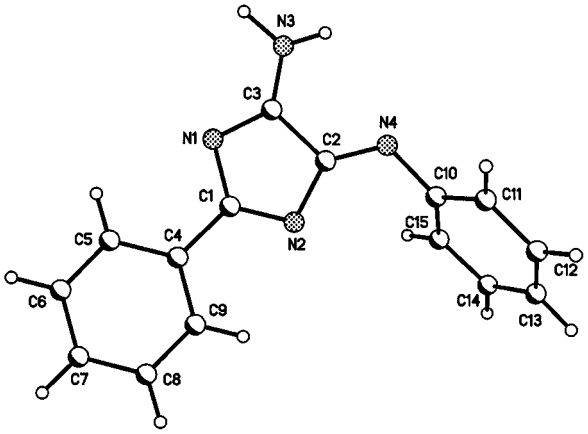
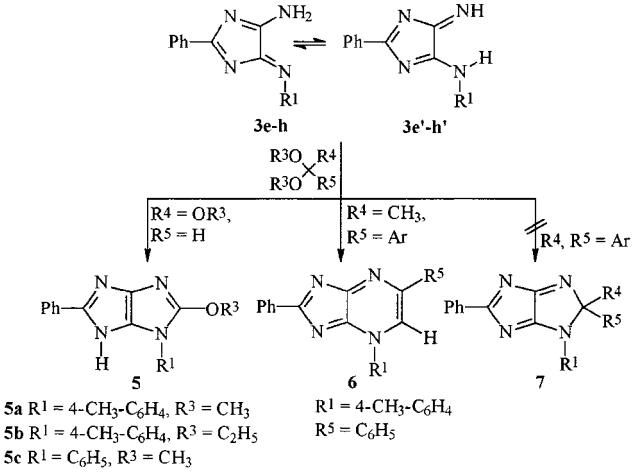


Figure 2. Perspective drawing of **3f**; the numbering corresponds to that used for the X-ray analysis; selected distances [A] and angles [°]: C3–N1 1.329(2), N1–C1 1.408(2), C1–N2 1.329(2), N2–C2 1.399(2), C2–C3 1.511(2), C3–N3 1.319(2); C3–N1–C1 102.7 (1), C1–N2–C2 103.3(1), N2–C2–N4 131.1(1), N1–C3–N3 127.3(1)

In analogy to the aliphatic derivatives, the hydrazino-substituted imidazole **3i** could be isolated upon treatment of **1a** with *N*,*N*-dimethylhydrazine. 2D NMR experiments show a stronger fixation of the NH protons on the aryl-substituted nitrogen in **3i**.

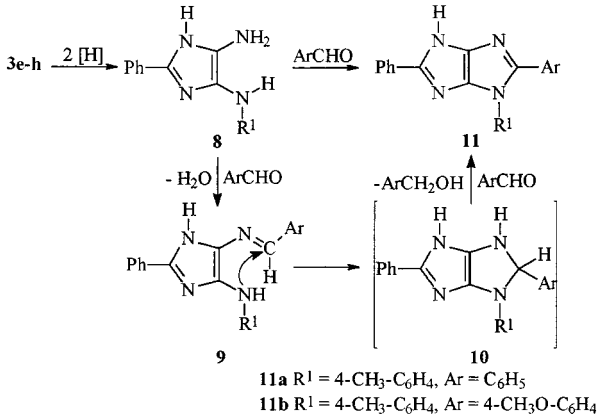
In order to exploit the utility of 4*H*-imidazoles in the synthesis of fused imidazo heterocycles, dinucleophiles were treated with **1**. Neither aromatic diamines such as *o*-phenylenediamine nor aliphatic derivatives such as ethylenediamine were found to react with **1a** in an exchange reaction. In the first case, as a result of benzamidine elimination, 2,3-diaminoquinoxalines could be isolated and characterized. Such quinoxalines are, however, more easily obtained by aminolysis of 2,3-dichloroquinoxaline or by cyclization of *o*-phenylenediamine with bis(imidoyl) chlorides of oxalic acid.[10] In contrast to these results, mixed substituted derivatives of types **3e–h** were expected to be more suitable for the synthesis of fused systems. Initial attempts to prepare bicyclic compounds involving the π-bond system of **1** using bis-electrophilic building blocks such as oxalyl chloride were fruitless. Applying these findings to the modification of tetraazafulvalenes,[11] however, we succeeded in reacting less electrophilic orthoesters with **1** to give the imidazo[4,5-*d*]imidazoles **5** (Scheme 2).



Scheme 2

An unexpected complex redox process ensued when acetophenone dimethylacetal was employed as the cyclization partner. A new 4*H*-imidazo[4,5-*b*]pyrazine **6** was obtained, in which the methyl group of the acetal had been transformed into a methine unit of a six-membered ring. The π systems of such conjugated bicycles are isoelectronic with that of azulene and hence they can be classified as pseudoazulenes.[12] Compounds of type **6** show relatively hypsochromic absorptions at $\lambda_{max} = 406$ nm in their UV/vis spectra, similar to those observed for the structurally isomeric purines.[13] The high regioselectivity of the cyclization with respect to the CH group of the pyrazine system was confirmed by 2D NMR experiments. All attempts to synthesize precursors of dihydrotetraazapentalenes of type **7** by using, for example, benzophenone dimethylacetal as the cyclization reagent were unsuccessful.

As observed for the parent compounds of type **1**,[14] it was found that derivatives **3e–h** could easily be reduced with sodium dithionite, ascorbic acid, or Zn/HCl. In the presence of air, the strongly fluorescent leuco compounds **8** were quickly reoxidized with formation of the starting material **1** and hydrogen peroxide. Treatment of **8** with aromatic aldehydes resulted in condensation reactions that yielded azomethines of type **9**; these products could not be isolated, but were detectable by TLC. Compounds **9** may undergo cyclization to give the bicycles **10** (Scheme 3). Because of the well-known lability of the electron-rich tetraaminoethene substructure with respect to oxidative processes,[15] the derivative **11** was the finally isolated product. The reduction equivalents are transferred to the carbonyl system in a Cannizzaro-like redox process. On using an excess of benzaldehyde, benzyl alcohol could be detected by GC. The ^{1}H-NMR spectra of compounds **11** feature a singlet due to the XH proton at $\delta = 12.94$, further confirming the occurrence of redox disproportionation had taken place. Furthermore, the structure of the imidazo[4,5-*d*]imidazole **11b** was confirmed by X-ray analysis (Figure 3). In contrast to the alkyloxy derivatives **5a–c**, in the solid-state structure of **11b**



Scheme 3

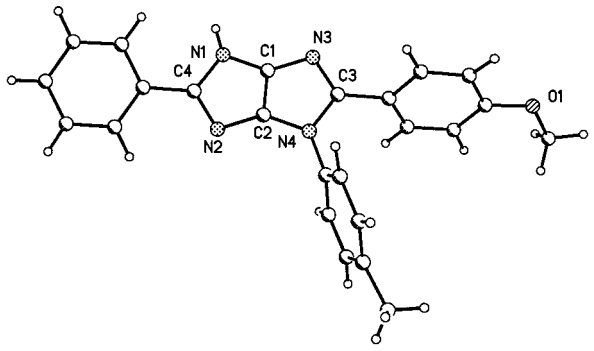


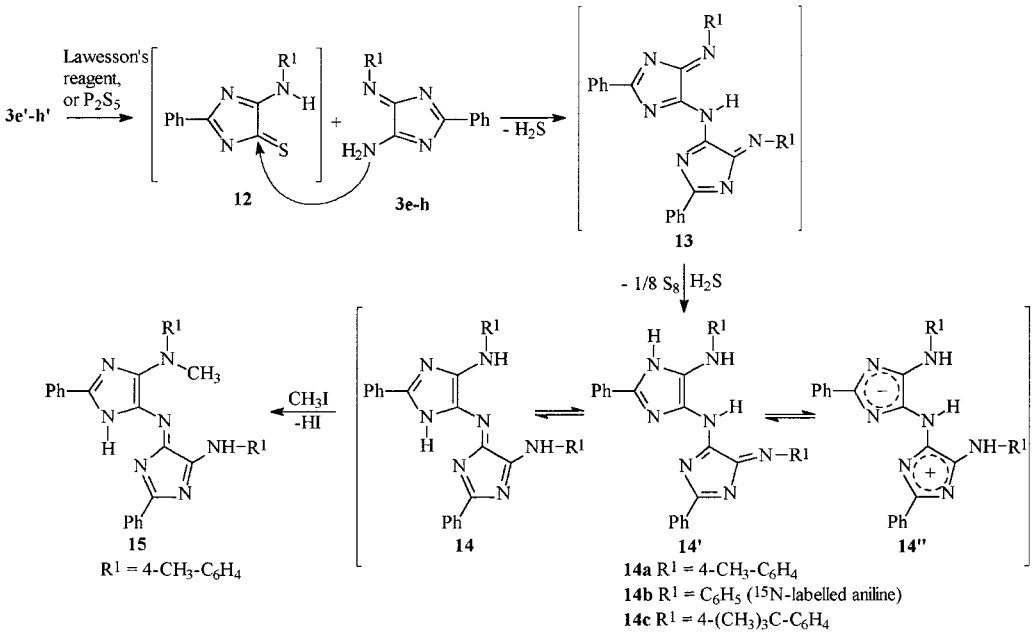
Figure 3. Representation of the molecular structure of **11b**; the numbering corresponds to that used for the X-ray analysis; selected distances [Å] and angles [°]: C1–C2 1.361(2), C2–N2 1.369(2), N2–C4 1.369(2), C4–N1 1.386(2), N1–C1 1.376(2), C1–N3 1.374(2), N3–C3 1.346(2), C3–N4 1.398(2), N4–C2 1.389(2); C4–N2–C2 102.2(1), C4–N1–C1 105.2(1), C1–N3–C3 102.9(1), C3–N4–C2 105.6(1)

the NH proton is held in position by strong hydrogen bonds, which lead to dimeric units with a head-to-tail arrangement.

In order to obtain new thioxo compounds, further experiments were carried out in which **3e–h** were reacted with sulfur transfer reagents. In all cases, deep-green compounds were isolated as the main products when P_2S_5 or the more advantageous Lawesson's reagent was used. Elemental analyses and MS data showed that these compounds were sulfur-free, thus indicating that an unexpected reaction had taken place. On the basis of high-resolution MS data, we concluded that imidazo-substituted 4*H*-imidazoles **14** had been formed (Scheme 4). Due to the dynamic nature of compounds **14**, a structural determination by ^{1}H NMR was not possible, not even at low temperatures. A ^{15}N-labelled derivative (**14b**) showed signal coalescence at room temperature that was only partly resolved at –60 °C. The appearance of a twofold set of signals as well as of five discrete signals for the five different NH protons (three doublets due to ^{15}N-^{1}H coupling; two singlets) indicates that **14** exists in a temperature-dependent equilibrium mixture of tautomeric forms.

Heating the samples up to 60 °C resulted in spectra of dynamic structures, in which the aromatic rings of the two heterocycles give rise to only a single set of signals and the NH proton signals are not separate. The remarkable bathochromic UV/vis absorption observed (**14a**: λ_{max} = 662 nm) is due to the similarity of **14a** to the push-pull chromophores found in indigoid systems. In the present case, the aza nitrogen connects the π-systems of the two diazafulvene units. Electron delocalization is thus possible over the entire system.

The tautomerism observed between **3e–h** and **3e′-h′** (Scheme 2) is most probably central to the formation of **14**.



Scheme 4

We therefore propose that Lawesson's reagent first reacts with **3e′-h′** to form the non-isolable thioxo derivative **12**. Indeed, a few thionation reactions of substituted imines with H_2S have been reported, giving comparable results with those presented here.[16] A subsequent condensation reaction between the thioxo group and the primary amino group in **3e–h** leads to **13** under elimination of hydrogen sulfide. The sulfide finally acts as a reducing agent towards the 4*H*-imidazole system in **13**, leading to the more stable **14**. In independent parallel experiments, it was shown that H_2S is capable of reducing 4*H*-imidazoles of type **1** in a smooth reaction, thereby forming 4,5-diaminoimidazoles. We will report on this selective reduction and its application to aromatic and aliphatic thiols in a forthcoming article. All attempts to oxidize **14** to the bridged 4*H*-imidazoles **13** using various oxidizing agents were unsuccessful. Similarly, it proved impossible to reduce **14** to two bridged imidazoles. It is thus obvious that these compounds are members of a new covalently-bonded redox system characterized by highly dynamic molecules. Methylation of **14** using methyl iodide occurs under mild conditions with elimination of hydrogen iodide. The ^{1}H-NMR spectrum of the methylation product **15** clearly shows a restriction of exchange processes (four different aromatic spin systems are present at room temperature). The existence of cross-peaks between the aromatic tolyl protons and the introduced methyl group in NOESY experiments is indicative of exocyclic substitution.

Experimental Section

General: All reagents were of commercial quality (Aldrich, Fluka, Merck) and were used as received. ^{15}N-labelled aniline (99%) was purchased from MSD isotopes. Solvents were dried and purified using standard techniques. – Reactions were monitored by TLC on plastic plates coated with neutral alumina containing a fluorescence indicator (Polygram ALOX N/UV$_{254}$ from Macherey–Nagel). – Flash chromatographic separations were carried out on neutral alumina (Merck, neutral aluminium oxide 90, activity grade V, particle size 0.063–0.2 mm, 70–230 mesh ASTM). – Melting points were measured with a Galen III (Boetius system) from Cambridge Instruments and are uncorrected. – UV/vis spectra were recorded on a Perkin–Elmer Lambda 19 spectrophotometer. – The ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker DRX 400 (400 MHz) and Bruker AC 250 (250 MHz) spectrometers (^{1}H NMR shifts relative to ^{1}H signals of the solvent). – MS spectra were measured on a Finnigan MAT SAQ 710 mass spectrometer. – Elemental analyses were carried out in-house using a LECO CHNS 932 automatic analyzer.

Crystal Structure Determination. – Data Collection: The intensity data for the compounds were collected on a Nonius KappaCCD diffractometer using graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption.[17] The structures were solved by direct methods (SHELXS[18]) and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97).[18] The hydrogen atoms were located by difference Fourier synthesis and refined isotropically. All non-hydrogen atoms were refined anisotropically.[19] XP (Siemens Analytical X-ray Instruments, Inc.) was used for structure representations.

Crystal Data for 3f:[20] $C_{15}H_{12}N_4CH_3CN$, M_r = 289.34 gmol^{-1}, orange prism, size 0.32 × 0.30 × 0.22 mm^3, monoclinic, space group $P2_1/c$, a = 5.4438(2), b = 20.1625(7), c = 13.9434(5) Å, β = 98.211(2)°, V = 1514.75(9) Å^3, T = –90 °C, Z = 4, ρ_{calcd} = 1.269 gcm^{-3}, μ (Mo-K_α) = 0.8 cm^{-1}, F(000) = 608, 5795 reflections in h(–6/6), k(–25/25), l(–17/17), measured in the range 3.37° Θ 26.38°, completeness Θ_{max} = 99.5%, 3092 independent reflections, R_{int} = 0.030, 2299 reflections with $F_o > 4\sigma(F_o)$, 259 parameters, $R1_{obs}$ = 0.044, wR^2_{obs} = 0.105, $R1_{all}$ = 0.068, wR^2_{all} = 0.114, GOOF = 1.046, largest difference peak and hole: 0.176/–0.198 eÅ^3.

Crystal Data for 4c:[20] $C_{11}H_{12}N_4$, M_r = 200.25 gmol^{-1}, colourless prism, size 0.30 × 0.20 × 0.10 mm^3, triclinic, space group P-1, a = 7.5225(7), b = 7.9419(7), c = 10.0397(7) Å, α = 70.007(4), β = 84.091(5), γ = 66.893(4)°, V = 518.10(8) Å^3, T = –90 °C, Z = 2, ρ_{calcd} = 1.284 gcm^{-3}, μ (Mo-K_α) = 0.82 cm^{-1}, F(000) = 212, 3772 reflections in h(–9/9), k(–10/10), l(–13/13), measured in the range 3.42° Θ 27.48°, completeness Θ_{max} = 97.8%, 2318 independent reflections, R_{int} = 0.035, 1761 reflections with $F_o > 4\sigma(F_o)$, 188 parameters, $R1_{obs}$ = 0.049, wR^2_{obs} = 0.113, $R1_{all}$ = 0.0705, wR^2_{all} = 0.123, GOOF = 1.023, largest difference peak and hole: 0.183/–0.186 eÅ^3.

Crystal Data for 11b:[20] $C_{24}H_{20}N_4O$, M_r = 380.44 gmol^{-1}, colourless prism, size 0.30 × 0.20 × 0.10 mm^3, monoclinic, space group $P2_1/c$, a = 7.9494(2), b = 11.7431(3), c = 20.909(1) Å, β = 93.754(2)°, V = 1947.7(1) Å^3, T = –90 °C, Z = 4, ρ_{calcd} = 1.297 gcm^{-3}, μ(Mo-K_α) = 0.82 cm^{-1}, F(000) = 800, 8319 reflections in h(–10/10), k(–13/14), l(–27/27), measured in the range 3.10° Θ 27.47°, completeness Θ_{max} = 98.4%, 4405 independent reflections, R_{int} = 0.042, 3047 reflections with $F_o > 4\sigma(F_o)$, 342 parameters, $R1_{obs}$ = 0.058, wR^2_{obs} = 0.122, $R1_{all}$ = 0.099, wR^2_{all} = 0.137, GOOF = 1.046, largest difference peak and hole: 0.197/–0.278 eÅ^{-3}.

General Procedure for Nucleophilic Substitution Reactions of the 4*H*-Imidazoles 1. – Method A: To a solution of **1** (1.0 mmol) in THF (30 mL), a catalytic amount (3 drops) of concentrated hydrochloric acid was added. An immediate colour change was observed owing to formation of the protonated heterocycle **2**. Then, either an excess of a monofunctional amine (5.0 mmol) or *o*-phenylenediamine (1.5 mmol) was added. The resulting mixture was heated under reflux and the progress of the reaction was monitored by TLC (typically, a mixture of **3** and **4** was detected). Reactions were generally allowed to proceed for 1–4 h. After filtration, the filtrate was concentrated in vacuo and the residue was purified either by column chromatography (eluent: ethyl acetate/*n*-heptane, 1:5) or by recrystallization from acetone/heptane, to yield the products **3** and/or **4**.

Method B: To a solution of **1** (1.0 mmol) in THF (30 mL), aqueous ammonia solution (25%, 20 mL) or an aqueous solution of the appropriate alkylamine (33%, 10 mL) was added. The reaction mixture was then heated under reflux with vigorous stirring. After completion of the reaction (TLC control), the solution was cooled to room temperature. The organic layer was separated, and the aqueous layer was washed with two 50 mL portions of ethyl acetate. The combined organic fractions were then dried over anhydrous Na_2CO_3, filtered, and the solvent was removed in vacuo. The residue was chromatographed on alumina using ethyl acetate/heptane as eluent, yielding compounds **3e–h** and **4c**,**d**. In the case of **3e**, the combined organic layers were concentrated and the product was precipitated by adding *n*-heptane; this material proved sufficiently pure to be used without further purification.

5-[4-(Methoxy)phenylamino]-2-phenyl-4-(4-tolylimino)-4*H*-imidazole (3a): Method A; yield: 0.18 g (49%), red crystals; m.p.

188 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.56 (d, 2 H), 8.06 (d, 2 H), 7.89 (d, 2 H), 7.51 (m, 3 H), 7.25 (d, 2 H), 6.97 (d, 2 H), 5.26 (br. s, 1 H, NH), 3.85 (s, 3 H, OCH_3), 2.37 (s, 3 H, CH_3-Tol). – ^{13}C NMR (62 MHz, $CDCl_3$): δ = 187.7, 164.8, 159.2, 135.6, 133.5, 133.6, 132.2, 130.5, 130.4, 129.8, 129.8, 128.5, 127.6, 123.6, 121.7, 55.5, 21.2. – MS: *m*/*z* (%) = 369 [M + H$^+$] (100), 337 (10). – UV/vis (CH_2Cl_2): λ_{max} (lg ε) = 273 nm (4.26), 341 (4.16), 414 (4.09), 494 (4.32), 522 (4.22). – $C_{23}H_{20}N_4O$ (368.42): calcd. C 74.98, H 5.47, N 15.20; found C 75.10, H 5.89, N 15.09.

5-[4-(Dimethylamino)phenylamino]-2-phenyl-4-(4-tolylimino)-4*H*-imidazole (3b): Method A; yield 0.21 g (56%) purple crystals; m.p. 185–186 °C. – ^{1}H NMR (250 MHz, [D$_8$]THF): δ = 8.52 (d, 2 H), 8.16 (d, 2 H), 8.03 (d, 2 H), 7.52 (m, 3 H), 7.21 (d, 2 H), 6.80 (d, 2 H), 4.71 (br. s, 1 H, NH) 3.06 [s, 6 H, $N(CH_3)_2$], 2.35 (s, 3 H, CH_3). – ^{13}C NMR (62 MHz, [D$_8$]THF): δ = 151.4, 146.8, 134.2, 133.1, 130.6, 130.1, 123.0, 129.0, 125.7, 115.1, 112.7, 40.3, 21.1. – MS: *m*/*z* (%) = 382 [M + H$^+$] (100), 337 (15), 269 (8), 108 (38). – UV/vis (CH_2Cl_2): λ_{max} (lg ε) = 292 nm (4.18), 460 (3.81), 574 (4.29). – $C_{24}H_{23}N_5$ (381.46): calcd. C 75.57, H 6.08, N 18.36; found C 76.07, H 6.06, N 18.00.

5-Amino-2-phenyl-4-(4-tolylimino)-4*H*-imidazole (3e): Method B; yield 0.23 g (88%), yellow crystals; m.p. 178–180 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.34 (d, 2 H, *o*-Ph), 7.85 (d, 2 H, Tol), 7.59 (t, 1 H, *p*-Ph), 7.49 (t, 2 H, *m*-Ph), 7.23 (d, 2 H, Tol), 2.39 (s, 3 H, CH_3-Tol). – ^{13}C NMR (62 MHz, $CDCl_3$): δ = 186.6, 172.3, 159.8, 143.8, 138.5, 133.5, 131.7, 129.9, 129.6, 128.6, 127.2, 21.4. – MS: *m*/*z* (%) = 263 [M + H$^+$] (100), 247 [M – NH_2^+] (9), 117 (15), 89 (10). – UV/vis ($CHCl_3$): λ_{max} (lg ε) = 311 nm (4.14), 444 (3.98). – $C_{16}H_{14}N_4$ (262.30): calcd. C 73.26, H 5.38, N 21.36; found C 73.18, H 5.76, N 21.24.

5-Amino-2-phenyl-4-(phenyl-^{15}N-imino)-4*H*-imidazole (3f): Method B; yield 0.20 g (82%), yellow crystals; m.p. 193 °C. – ^{1}H NMR (400 MHz, [D$_8$]THF): δ = 8.37 (d, *J* = 7.12 Hz, 2 H), 7.87 (d, *J* = 7.87 Hz, 2 H), 7.56 (t, *J* = 7.50 Hz, 1 H), 7.46 (t, *J* = 7.50 Hz, 2 H), 7.37 (t, *J* = 7.86 Hz, 2 H), 7.19 (t, *J* = 7.59 Hz, 1 H). – ^{1}H NMR (400 MHz, [D$_8$]THF, 258 K): δ = 8.90 (br. s, 1 H, NH), 8.57 (br. s, 1 H, NH). – ^{13}C NMR (100 MHz, [D$_8$]THF): δ = 174.7, 174.5, 148.3, 133.8, 133.7, 130.9, 129.2, 129.2, 129.0, 127.7, 127.6. – MS(EI): *m*/*z* (%) = 249 [M$^+$] (23), 242 (52), 121 (35), 104 (34), 94 (100). – UV/vis ($CHCl_3$): λ_{max} (lg ε) = 297 nm (4.16), 437 (3.76). – $C_{15}H_{12}N_3{}^{15}N$ (249.27): calcd. C 72.28, H 4.85, N 22.87; found C 71.63, H 5.14, N 22.05.

5-Amino-4-[4-(*tert*-butyl)phenylimino]-2-phenyl-4*H*-imidazole (3g): Method B; yield 0.23 g (76%), yellow crystals; m.p. 184–186 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.34 (d, 2 H), 7.87 (d, 2 H), 7.59 (t, 1 H), 7.48 (t, 2 H), 7.45 (d, 2 H), 1.34 (s, 9 H). – ^{13}C NMR (62 MHz, $CDCl_3$): δ = 186.7, 172.4, 160.0, 151.5, 143.7, 133.5, 131.6, 130.0, 128.6, 126.8, 125.9, 34.8, 31.3. – MS: *m*/*z* (%) = 305 [M + H$^+$] (100), 289 [M – NH_2^+] (8), 249 (20), 247 [M – $C(CH_3)_3$] (35), 150 (24), 134 (15), 94 (27). – UV/vis ($CHCl_3$): λ_{max} (lg ε) = 313 nm (4.22), 442 (4.10). – $C_{19}H_{20}N_4$ (304.38): calcd. C 75.00, H 6.62, N 18.41; found C 75.36, H 6.82, N 18.01.

5-Amino-4-[4-(methoxy)phenylimino]-2-phenyl-4*H*-imidazole (3h): Method B; yield 0.16 g (57%), yellow crystals; m.p. 188 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.36 (d, 2 H), 8.04 (d, 2 H), 7.57 (t, 1 H), 7.47 (t, 2 H), 6.95 (d, 2 H). – ^{13}C NMR (62 MHz, $CDCl_3$): δ = 186.0, 172.4, 160.0, 158.4, 139.8, 133.4, 131.7, 129.9, 129.7, 128.6, 114.3, 55.5. – MS: *m*/*z* (%) = 279 [M + H$^+$] (100), 247 (8), 133 (3). – UV/vis ($CHCl_3$): λ_{max} (lg ε) = 274 nm (4.17), 294 (4.17), 458 (4.24). – $C_{16}H_{14}N_4O$ (278.29): calcd. C 69.05, H 5.07, N 20.13; found C 68.45, H 5.38, N 19.70.

5-(*N*′,*N*′-Dimethylhydrazino)-2-phenyl-4-(4-tolylimino)-4*H*-imidazole (3i): Method A; yield: 0.26 g (85%), yellow crystals; m.p. 177–178 °C. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.28 (s, 1 H, NH), 8.20 (d, 2 H), 7.98 (d, 2 H), 7.45 (m, 3 H), 7.15 (d, 2 H), 3.85 [s, 6 H, $N(CH_3)_2$], 2.27 (s, 3 H, CH_3-Tol). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 164.3, 142.0, 137.8, 134.7, 132.9, 131.3, 130.6, 129.2, 129.1, 119.3, 47.6, 22.0. – MS (DEI): *m*/*z* (%) = 305 [M$^+$] (31), 261 [M – $N(CH_3)_2^+$] (83), 247 [M – $NHN(CH_3)_2$] (100), 129 (14), 104 (13), 91 (91). – UV/vis (CH_2Cl_2): λ_{max} (lg ε) = 277 nm (4.32), 341 (4.32), 434 (4.25). – $C_{18}H_{19}N_5$ (305.37): calcd. C 70.80, H 6.27, N 22.93; found C 70.60, H 6.53, N 21.93.

5-[4-(Methoxy)phenylamino]-4-[4-(methoxy)phenylimino]-2-phenyl-4*H*-imidazole (4a): Method A; yield 0.34 g (88%), red crystals. Spectral data were in agreement with those reported in ref.[1]

5-[4-(Dimethylamino)phenylamino]-4-[4-(dimethylamino)-phenylimino]-2-phenyl-4*H*-imidazole (4b): Method A; yield 0.33 g (81%), blue crystals. Spectral data were in agreement with those reported in ref.[1]

5-Methylamino-4-methylimino-2-phenyl-4*H*-imidazole (4c): Method B; yield 0.11 g (58%), yellow crystals; m.p. 147 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.39 (d, 2 H), 7.52 (m, 3 H), 5.47 (br. s, 1 H, NH), 3.42 (s, 6 H). – ^{13}C NMR (62 MHz, $CDCl_3$): δ = 186.8, 167.9, 133.2, 132.1, 129.9, 128.4, 119.8, 34.7. – MS: *m*/*z* (%) = 201 [M + H$^+$] (100), 145 (3), 103 (12). – UV/vis (CH_2Cl_2): λ_{max} (lg ε) = 300 nm (4.40), 403 (3.62). – $C_{11}H_{12}N_4$ (200.24): calcd. C 65.98, H 6.04, N 27.98; found C 65.83, H 6.17, N 27.85.

5-Ethylamino-4-ethylimino-2-phenyl-4*H*-imidazole (4d): Method B; yield 0.12 g (53%), yellow crystals; m.p. 134–137 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, 2 H), 7.54 (t, 1 H), 7.45 (t, 2 H), 5.52 (s, 1 H, NH), 3.79 (q, ^3J = 7.30 Hz, 4 H, CH_2), 1.30 (t, ^3J = 7.32 Hz, 6 H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.8, 166.7, 133.1, 132.2, 129.9, 128.4, 42.6, 15.2 – MS (DEI): *m*/*z* (%) = 228 [M$^+$] (100), 213 (9), 200 (27), 159 (14), 129 (25), 103 (57). – $C_{13}H_{16}N_4$ (228.30): calcd. C 68.39, H 7.06, N 24.54; found C 68.02, H 7.12, N 24.84.

General Procedure for the Synthesis of Imidazo[4,5-*d*]imidazoles 5: A mixture of **3e–h** (1.0 mmol) and 30 mL of the appropriate trialkyl orthoformate was heated under reflux for 3 h. The excess ester was then removed in vacuo and the residue was purified by column chromatography eluting with a 5:1 mixture of ethyl acetate and *n*-heptane. The eluate was concentrated (to ca. 5 mL) and then kept at –78 °C overnight, whereupon compounds **5** were deposited as colourless crystalline solids.

2-Methoxy-5-phenyl-1-(4-tolyl)-1,6-dihydroimidazo[4,5-*d*]imidazole (5a): Yield 0.19 g (66%), colourless crystals; m.p. 234 °C. – ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 10.8 (br. s, 1 H, NH), 7.85 (d, 2 H), 7.44 (d, 2 H), 7.37 (t, 2 H), 7.28 (d, 2 H), 7.26 (t, 1 H), 3.98 (s, 3 H, OCH_3), 2.41 (s, 3 H, CH_3). – ^{13}C NMR (62 MHz, [D$_6$]DMSO): δ = 152.6, 141.1, 135.2, 134.1, 133.1, 131.6, 129.7, 128.7, 127.1, 124.1, 121.5, 120.3, 57.2, 20.5. – MS: *m*/*z* (%) = 305 [M + H$^+$] (100), 269 (85), 186 (2), 118 (4). – $C_{18}H_{16}N_4O$ (304.33): calcd. C 71.03, H 5.29, N 18.41; found C 70.49, H 5.57, N 18.21.

2-Ethyloxy-5-phenyl-1-(4-tolyl)-1,6-dihydroimidazo[4,5-*d*]imidazole (5b): Yield 0.23 g (72%), colourless crystals; m.p. 212–214 °C. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.80 (s, 1 H, NH), 7.90 (d, 2 H), 7.75 (d, 2 H), 7.40 (t, 2 H), 7.34 (d, 2 H), 7.27 (t, 1 H), 4.48 (q, ^3J = 6.88 Hz, 2 H), 2.35 (s, 3 H), 1.39 (t, ^3J = 6.72 Hz, 3 H). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.1, 141.9, 135.4, 134.2, 133.2, 131.7, 130.8, 129.5, 128.6, 127.1, 124.5, 122.1, 66.4, 21.0,

14.2. – MS (DEI): *m/z* (%) = 318 [M$^+$] (40), 289 (17), 247 (8), 186 (30), 118 (100), 91 (28). – $C_{19}H_{18}N_4O$ (318.38): calcd. C 71.68, H 5.70, N 17.60; found C 71.31, H 6.05, N 16.86.

2-Methoxy-1,5-diphenyl-1,6-dihydroimidazo[4,5-*d*]imidazole (5c): Yield 0.18 g (63%), colourless crystals; m.p. 206 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.32 (s, 1 H, NH), 7.90 (d, 2 H), 7.66 (d, 2 H), 7.51–7.35 (m, 3 H), 7.31–7.17 (m, 3 H), 4.10 (s, 3 H). – ^{13}C NMR (62 MHz, $CDCl_3$): δ = 136.3, 134.5, 131.4, 129.3, 128.9, 126.1, 125.6, 124.7, 122.1, 119.8, 57.2. – MS: *m/z* (%) = 291 [M + H$^+$] (64), 241 (100), 120 (4), 93 (10). – $C_{17}H_{14}N_4O$ (290.31): calcd. C 70.33, H 4.86, N 19.30; found C 70.13, H 5.28, N 18.64.

2,6-Diphenyl-4-(4-tolyl)-4*H*-imidazo[4,5-*b*]pyrazine (6): A solution of **3e** (0.26 g, 1.0 mmol) and acetophenone dimethylacetal (5 mL) in THF (30 mL) was stirred under reflux for 5 h. The solvent was then removed in vacuo and the residue was chromatographed using *n*-heptane/ethyl acetate (6:1) as eluent. Yield 0.22 g (62%), yellow crystals; m.p. 247–249 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (d, 2 H), 8.07 (d, 2 H), 8.01 (s, 1 H, CH), 7.79 (d, 2 H), 7.47 (m, 8 H), 2.50 (s, 3 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9, 163.5, 144.2, 141.9, 138.1, 137.2, 134.4, 132.6, 131.5, 130.7, 130.3, 130.1, 129.5, 127.5, 125.9, 120.7, 118.6, 22.3. – MS: *m/z* (%) = 363 [M + H$^+$] (100), 269 (4), 181 (3). – UV/vis (CH_2Cl_2): λ_{max} (lg ε) = 280 nm (4.33), 406 (4.24). – $C_{24}H_{18}N_4$ (362.41): calcd. C 79.54, H 5.01, N 15.46; found C 79.24, H 5.27, N 14.58.

General Procedure for the Synthesis of Imidazo[4,5-*d*]imidazoles 11: In a Schlenk vessel, **3e–h** (1.0 mmol) was dissolved in 30 mL of THF under argon and reduced either by heating the solution with 0.5 g of Zn and 3 drops of concentrated hydrochloric acid, or by passing a steady stream of H_2S through the reaction mixture for 1 h. In both cases, a clear colourless solution was obtained, to which an excess of the appropriate aromatic aldehyde (1.6 mmol) was added. Stirring at room temperature was continued for 2 h, in the course of which the colour of the solution turned to yellow. The solvent was then removed in vacuo and the residue was subjected to chromatography eluting with ethyl acetate/*n*-heptane, 1:1. In the course of this procedure, a cyclization occurred leading to a colourless solution with a strong blue fluorescence. This solution was concentrated (to ca. 5 mL) and then kept at –78 °C overnight, whereupon **11** was deposited as a crystalline solid.

2,5-Diphenyl-1-(4-tolyl)-1,4-dihydroimidazo[4,5-*d*]imidazole (11a): Yield 0.27 g (78%), colourless crystals; m.p. 311 °C. – ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 12.9 (br. s, 1 H, NH), 7.94 (t, 2 H), 7.59 (t, 1 H), 7.50–7.40 (m, 11 H), 2.37 (s, 3 H). – ^{13}C NMR (62 MHz, [D$_6$]DMSO): δ = 167.5, 145.9, 145.5, 137.5, 134.2, 132.6, 131.1, 130.1, 129.2, 128.8, 128.5, 128.3, 128.2, 128.1, 126.0, 124.8, 20.7. – MS (DEI): *m/z* (%) = 350 [M$^+$] (100), 143 (21), 122 (47), 117 (83), 91 (46), 77 (58). – $C_{23}H_{18}N_4$ (350.42): calcd. C 78.83, H 5.18, N 15.99; found C 77.87, H 5.52, N 15.59.

2-[4-(Methoxy)phenyl]-5-phenyl-1-(4-tolyl)-1,4-dihydroimidazo[4,5-*d*]imidazole (11b): Yield 0.31 g (81%), colourless crystals; m.p. 320 °C. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.94 (s, 1 H, NH), 7.93 (d, 2 H), 7.42 (t, 2 H), 7.36–7.28 (m, 7 H), 6.88 (d, 2 H), 3.74 (s, 3 H), 2.37 (s, 3 H). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 159.2, 145.7, 145.3, 140.8, 137.4, 137.3, 134.4, 131.4, 130.1, 129.7, 128.8, 128.0, 126.0, 124.7, 123.6, 113.8. – MS: *m/z* (%) = 381 [M + H$^+$] (100), 134 (7), 89 (37). – $C_{24}H_{20}N_4O$ (380.45): calcd. C 75.77, H 5.30, N 14.73; found C 74.98, H 5.62, N 14.38.

General Procedure for the Synthesis of Diimidazolyl Derivative 14: To a solution of **3e–h** (1.0 mmol) in THF (30 mL), Lawesson's reagent (0.4 g, 1.0 mmol) was added. The resulting mixture was then stirred at 50 °C for 2 h, in the course of which a deep-turquoise colour developed. After completion of the reaction (TLC control), the solvent was evaporated and the residue was chromatographed using *n*-heptane/ethyl acetate (5:1) as eluent to give the pure products **14**.

Diimidazolyl Derivative 14a: Yield 0.18 g (73%), black crystals; m.p. 324 °C. – ^{1}H NMR (400 MHz, [D$_6$]DMSO, 333 K): δ = 8.26 (d, 4 H), 7.89 (d, 4 H), 7.59–7.51 (m, 6 H), 7.23 (d, 4 H), 2.32 (s, 6 H). – ^{1}H NMR (400 MHz, [D$_8$]THF, 223 K): δ = 13.78 (s, 1 H, NH), 12.23 (s, 1 H, NH), 10.45 (s, 1 H, NH), 9.09 (s, 1 H, NH), 8.93 (s, 1 H, NH), 8.38 (d, 4 H), 8.15 (d, 2 H), 8.01 (d, 2 H), 7.95 (d, 4 H), 7.78 (d, 2 H), 7.57–7.48 (m, 10 H), 7.21 (m, 6 H), 7.14 (d, 2 H), 2.33 (s, 12 H). – ^{13}C NMR (100 MHz, [D$_6$]DMSO, 338 K): δ = 158.1, 137.2, 133.4, 131.0, 130.1, 129.0, 128.6, 128.3, 128.3, 126.8, 120.1, 118.5, 19.9. – MS: *m/z* (%) = 510 [M + H$^+$] (100), 403 (31), 353 (7), 263 (8), 134 (13), 108 (41). – UV/vis ($CHCl_3$): λ_{max} (lg ε) = 310 nm (4.43), 662 (4.74). – $C_{32}H_{28}N_7$ (510.24): calcd. C 75.32, H 5.53, N 18.22; found C 75.82, H 5.54, N 18.29. – HR-MS (ESI): calcd. 510.2406; found 510.2404.

Diimidazolyl Derivative 14b: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 333 K): δ = 8.25 (d, 4 H), 7.99 (d, 4 H), 7.54 (m, 6 H), 7.40 (t, 4 H), 7.04 (t, 2 H). – ^{1}H NMR (400 MHz, [D$_8$]THF, 223 K): δ = 13.78 [d, $^1J(^{15}N,^1H)$ = 87.22 Hz, 1 H, ^{15}NH], 12.26 (s, 1 H, NH), 9.11 [d, $^1J(^{15}N,^1H)$ = 92.36 Hz, 1 H, ^{15}NH], 9.02 [d, $^1J(^{15}N,^1H)$ = 92.16 Hz, 1 H, ^{15}NH], 8.41 (t, 4 H), 8.16 (m, 4 H), 8.07 (d, 4 H), 7.59–7.38 (m, 16 H), 7.02 (m, 4 H). – $C_{30}H_{23}N_5{}^{15}N_2$ (483.56).

Diimidazolyl Derivative 14c: Yield 0.20 g (68%), black crystals; m.p. 264–266 °C. – ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 13.6 (br. s, 1 H, NH), 13.1 (br. s, 1 H, NH), 9.7 (br. s, 1 H, NH), 8.28 (br. m, 4 H), 7.99 (br. m, 4 H), 7.56 (br. m, 6 H), 7.45 (d, 4 H), 1.31 (s, 18 H). – MS: *m/z* (%) = 594 [M + H$^+$] (43), 305 (14), 153 (5), 150 (70), 122 (26), 104 (100), 94 (51). – UV/vis ($CHCl_3$): λ_{max} (lg ε) = 289 nm (4.25), 446 (3.85), 610 (4.35) – $C_{38}H_{37}N_7$ (593.74): calcd. C 76.86, H 6.28, N 16.51; found C 76.63, H 6.82, N 15.87.

Diimidazolyl Derivative 15: To a solution of **14a** (0.25 g, 0.5 mmol) in acetonitrile (10 mL), methyl iodide (0.5 mL) was added and the mixture was refluxed for 5 h. The solvent was then removed in vacuo and the residue was purified by column chromatography eluting with toluene/acetone, 3:1. Yield: 0.09 g (36%), black crystals. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, 2 H), 8.08 (d, 2 H), 7.55 (d, 2 H), 7.52–7.43 (m, 7 H), 7.32 (d, 2 H), 7.27 (d, 2 H), 7.16 (d, 2 H), 6.67 (s, 1 H, NH), 2.44 (s, 3 H), 2.33 (s, 3 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 158.8, 156.1, 153.6, 143.5, 141.4, 136.7, 135.5, 132.3, 132.2, 130.7, 130.4, 130.1, 129.8, 129.6, 128.9, 128.5, 127.9, 126.6, 126.0, 118.2, 41.1, 21.2, 20.8. – MS: *m/z* (%) = 524 [M + H$^+$] (100), 403 (11), 262 (4), 122 (13), 108 (5). – UV/vis ($CHCl_3$): λ_{max} (lg ε) = 310 nm (4.23), 425 (4.14), 654 (4.45). – $C_{33}H_{30}N_7$ (524.25): calcd. C 75.61, H 5.77, N 18.70; found C 75.42, H 5.48, N 19.10.

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[20] Further details of the crystal structure investigations are available on request from the director of the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax (internat.) +44 (0)1223 336033; E-mail: deposit@ccdc.cam.ac.uk] on quoting the depository nos. CCDC-132525 (**3f**), CCDC-132527 (**4c**), and CCDC-132526 (**11b**), the names of the authors, and the full journal citation.

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