Regioselective Anionic [3+2] Cyclizations of Isoxazole, Pyrazole and 1,2,4-Triazole Dinucleophiles − Efficient Synthesis of 2,4-Dihydroimidazo-[4,5-*b*]quinoxalines, 3*H*-Imidazo[1,2-*b*]pyrazoles and 5*H*-Imidazo[2,1-*c*]-[1,2,4]triazoles

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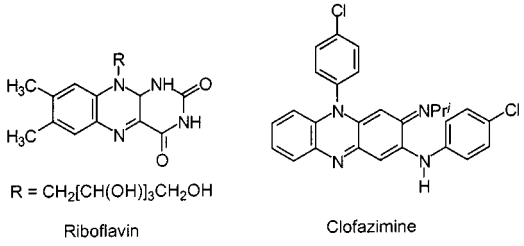
Regioselective cyclization reactions between oxaldiimidoyl dichlorides and 3-aminopyrazole and 3-amino-1,2,4-triazole provide convenient access to biologically relevant 3*H*-imidazo[1,2-*b*]pyrazoles and a 5*H*-imidazo[2,1-*c*][1,2,4]triazole. In contrast, treatment of 3-aminoisoxazoles with diimidoyl dichlorides results in a new and efficient anionic domino process for the synthesis of biologically relevant 2,4-dihydro-1*H*-imidazo[4,5-*b*]quinoxalines. All cyclizations proceed with high regioselectivities, which are explained with the aid of semiempirical computations.

Introduction

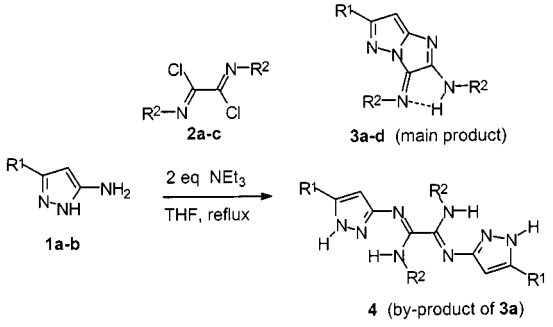
Leprosy is a common bacterial disease in many countries. 4,4′-Diaminodiphenylsulfone (dapsone), the antibiotic rifampin, and the substituted dihydrophenazine clofazimine are important drugs in leprosy therapy.[1,2] Clofazimine is effective against a number of diseases involving the autoimmune system.[3] However, it suffers from serious problems, such as crystal precipitation in the spleen[4] and bacterial resistance.[5] The development of suitable clofazimine analogues is therefore of pharmacological relevance.

In the preceding paper we studied[6] the regioselectivity of cyclizations of 2-methyl-, 2-amino-, 2-mercapto- and 2-hydroxybenzimidazoles with oxaldiimidoyl dichlorides.[7] These reactions afforded a variety of structurally interesting and biologically relevant benzimidazoles and diazabicyclo[2.2.1]heptanones. We have also studied cyclizations of oxaldiimidoyl dichlorides with 3-aminopyrazoles, 3-amino-1,2,4-triazoles and 3-aminoisoxazoles. In this context, we have recently developed a new anionic domino reaction which allows for a convenient synthesis of 2,4-dihydro-1*H*-imidazo[4,5-*b*]quinoxalines.[8,9] Here, we wish to report full details of our new cyclization reactions. This also includes semiempirical computations on some of the key structures, so as to explain the geometric preferences and the observed regioselectivities. The products prepared are of biological relevance since they constitute analogues of clofazimine (s. a.), riboflavin (vitamin B_2) and lumiflavin.



Results and Discussion

Our starting point was the reaction between 3-aminopyrazoles **1a**,**b** and oxaldiimidoyl dichlorides **2**. These reactions afforded the orange 3*H*-imidazo[1,2-*b*]pyrazoles **3a**−**d** in good yields (Scheme 1, Table 1). In case of the synthesis of **3a**, the colourless open-chained oxalamidine **4** could be isolated as a minor product. Several tautomeric structures for heterocycles **3a**−**d** are possible; the ^{1}H NMR spectra of **3a**−**d** exhibit low-field signals attributable to the N−H



Scheme 1. Cyclizations between 3-aminopyrazoles and oxaldiimidoyl dichlorides

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Table 1. Synthesis of **3a**−**d**

3	R^1	R^2	M.p. [°C][a]	Yield (%)[b]
a	H	C_6H_5	168−170	58
b	H	4-$CH_3C_6H_4$	177−179	47
c	CH_3	4-$CH_3C_6H_4$	155−156	63
d	H	4-$CH_3OC_6H_4$	144−146	69

[a] Uncorrected. − [b] Isolated yield.

protons (CH_2Cl_2: δ = 8.1). The absence of sharp N−H vibration bands supports the conjecture that tautomeric structures containing heterocyclic N−H bonds are not adopted. In solution, on the other hand, the tautomeric forms present are presumably those containing intramolecular hydrogen bonds (N−H···N). Heterocycles resembling **3** have proven active against a variety of cancer cell lines.[10]

The structure of oxalamidine **4** was independently confirmed by X-ray crystallography (Figure 1). The oxalic amidine subunit is twisted out of plane by 62.3°, due to the steric demand of the aryl groups. The *s-cis*-(*E*,*E*) configuration is stabilized by the two intramolecular hydrogen bonds N(4)−H···N(2) and N(4A)−H···N(2A) (1.908 Å). The amidine hydrogen atoms are located at the *N*-phenyl nitrogen atoms.

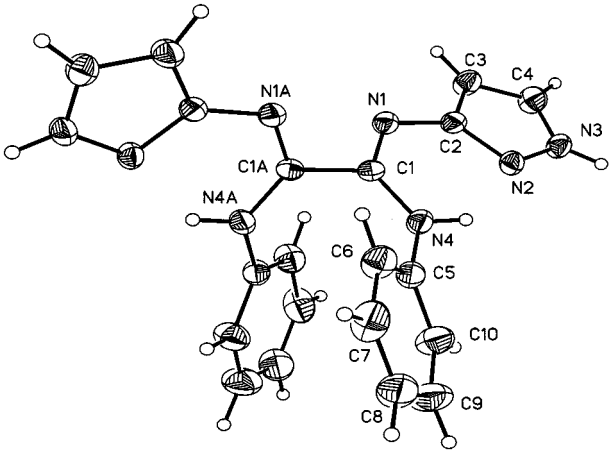
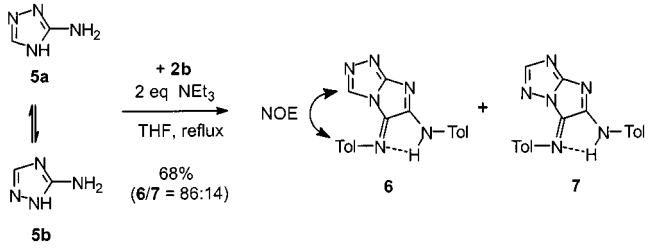


Figure 1. ORTEP plot of **4**; 50% probability thermal ellipsoids are shown for the non-hydrogen atoms; selected bond lengths [Å] and angles [°]: N(1)−C(1) 1.308(4), N(2)−C(2) 1.354(4), N(3)−C(4) 1.339(5), N(4)−C(5) 1.428(4), C(2)−C(3) 1.391(5), N(1)−C(2) 1.416(4), N(2)−N(3) 1.347(4), N(4)−C(1) 1.354(4), C(1)−C(1A) 1.511(6), C(3)−C(4) 1.367(5); N(1)−C(1)−N(4) 117.7(3). N(1)−C(1)−C(1A)−N(4A) 62.3, C(1)−N(1)−C(2) 120.5(3), C(1)−N(4)−C(5) 128.0(3)

3-Aminotriazole can exist as two tautomeric structures − **5a** and **5b** − and thus constitutes an ambident dinucleophile. Treatment of 3-amino-1,2,4-triazole with bis(tolylimidoyl) dichloride (**2b**) gave a separable 5:1 mixture of 5*H*-imidazo[2,1-*c*][1,2,4]triazole **6** and 6*H*-imidazo[1,2-*b*]-[1,2,4]triazole **7** (Scheme 2). The configuration of isomer **6** was proven by NOE measurements: An NOE interaction was detected between the heterocyclic CH group and a tolyl group. The regioselectivity can be understood as follows: The computed energy difference (AM1) is 4.2 kcal mol^{-1} in favour of **5a**; note that the amino group is nonplanar, as it is also found in other aromatic amines such as aniline (Figure 2).[11] The thermochemistry also favours **6** by 3.3 kcal mol^{-1}, most probably due to the absence of the long-range quadrupole C−H···π interaction found in **6**.[12] In addition, the bridgehead nitrogen atom of **7** is adjacent to an electron-withdrawing imino group and to an endocyclic, electron-withdrawing nitrogen atom. In case of **6**, the bridgehead nitrogen atom is adjacent to the imino group and to a carbon atom. In addition, the N−H group of **5a** is more nucleophilic than the N−H group of **5b**, due to the presence of an adjacent endocyclic nitrogen atom for **5b**.



Scheme 2. Cyclization between 3-aminotriazole and oxaldiimidoyl dichloride (**2b**)

First experiments involving treatment of oxaldiimidoyl dichlorides **2** with 3-aminoisoxazols **8** were unsuccessful; complex mixtures were obtained. Extension of the reaction times to 48−96 h was crucial for the formation of clean products. To our surprise, 2,4-dihydro-1*H*-imidazo[4,5-*b*]-quinoxalines **9a**−**f** were isolated in good yields (Scheme 3, Table 2). To the best of our knowledge, the heterocyclic subunit of compounds **9** has not to date been reported.[13] However, these compounds are of biological relevance, since they constitute analogues of known biologically active compounds such as riboflavin (vitamin B_2) and clofazimine (s. a.).

The regioselective and stereoselective formation of quinoxalines **9a**−**f** can be explained by initial formation of intermediate *i*, which is computed to be a probable, but high-energy (75.6 kcal/mol), intermediate along the reaction path to the global minimum **9a** on this part of the potential energy hypersurface (Figure 3). The N−O bond of intermediate *i* is cleaved to give the zwitterionic intermediate *ii*.[14] The aryl group is then attacked by the nitrogen atom to give intermediate *iii* and a tautomeric proton shift subsequently affords the final product. According to this proposed mechanism, the domino process involves five steps (double attack of the nitrogen atoms onto the imidoyl chloride groups, cleavage of the isoxazole moiety, nucleophilic attack of the nitrogen atom on the aryl group and a tautomeric proton shift). It is noteworthy that the exocyclic double bonds of **9a**−**f** form stereoselectively, presumably due to the formation of a stable intramolecular N−H···O hydrogen bond. Formation of the latter is possible for the (*E*) isomer, but not for the (*Z*) one.

2,4-Dihydro-1*H*-imidazo[4,5-*b*]quinoxalines are stable, intensely yellow compounds. The UV/Vis spectra of the qui-

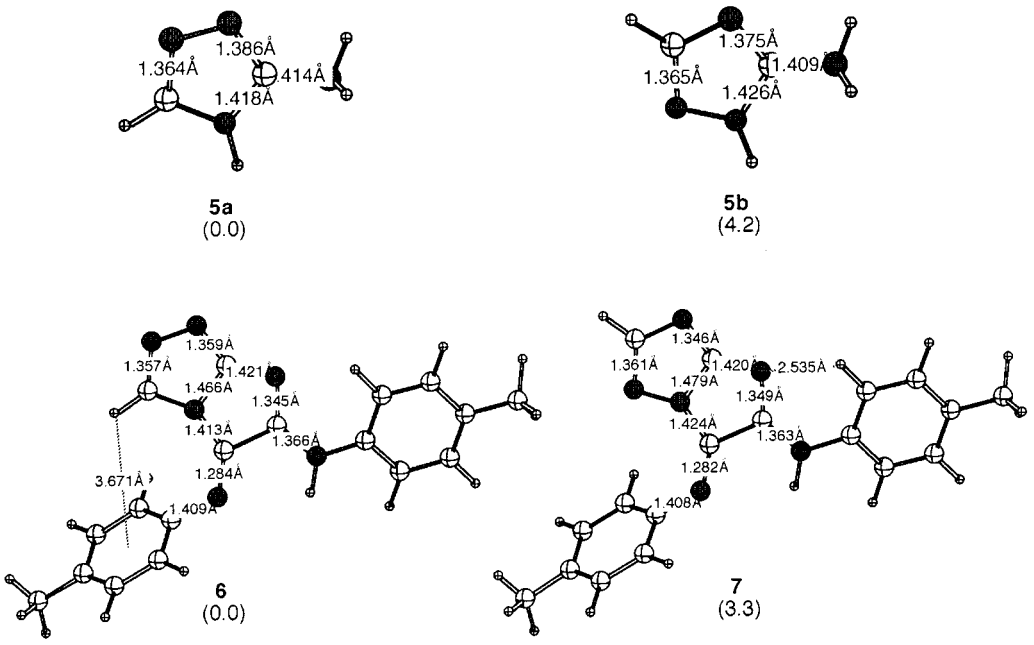
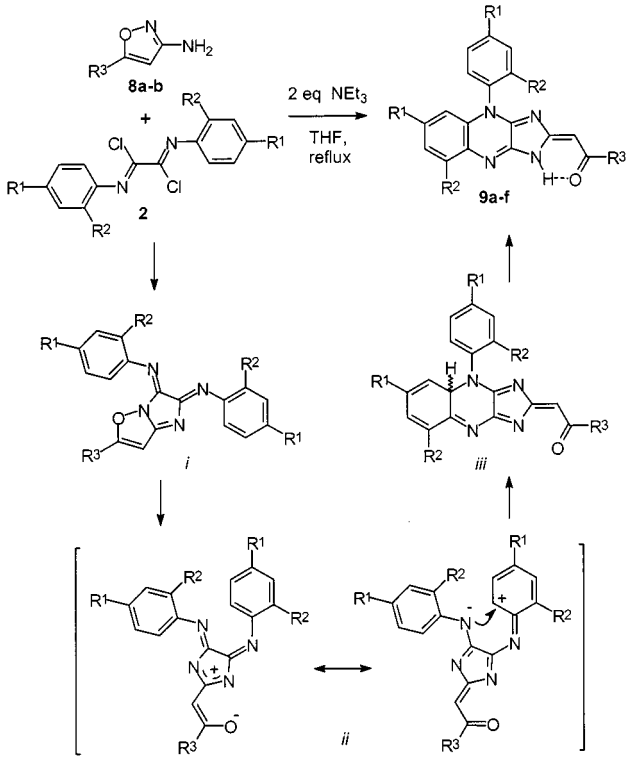


Figure 2. Regioselectivity of the reaction between 3-amino-1,2,4-triazole and oxaldiimidoyl dichlorides; computed AM1 geometries of **5a**, **5b**, **6** and **7**



Scheme 3. A possible mechanism for the domino reactions between 3-aminoisoxazoles and oxaldiimidoyl dichlorides

noxalines **9a**−**f** show six strong absorptions λ_1−λ_6 in the range from 255 to 465 nm. Bathochromic shifts are observed for **9e** and **9f**, which contain methoxy substituents. The structure of 2,4-dihydro-1*H*-imidazo[4,5-*b*]quinoxaline **9b** was independently confirmed by X-ray structure analysis (Figure 4). The (*E*) configuration of the exocyclic double bond and the presence of the intramolecular hydrogen bond N−H···O (2.08 Å) is clearly shown in the X-ray structure. The heterotricyclic subunit is planar; the *p*-tolyl group attached to N4 is twisted out of plane by 83.9°. The carbon−carbon bond C(2)−C(3) (1.45 Å) of the oxalic amidine subunit has single-bond character.

The structures of heterocycles **9a** and **9c**−**f** were elucidated from their spectroscopic data, by analogy with those of **9b**. An exocyclic double bond is present for all products **9a**−**f**, as indicated by the presence of a ^{1}H NMR signal in the δ = 5.55−5.83 range. The chemical shift of these protons depends only on the substituent R^3 (R^3 = Me: δ = 5.55−5.68; R^3 = *t*Bu: δ = 5.82−5.83), which indicates that the configuration of the exocyclic double bond is the same for all derivatives. This is also suggested by the presence of low-field signals (δ = 11.47−11.66) assigned to the N−H proton participating in intramolecular hydrogen bonding: N−H···O. For all heterocycles **9a**−**f**, high-field signals (^{13}C NMR) are observed for the exocyclic double bonds (δ = 88.5−93.4). Low-field signals (^{13}C NMR) attributable to the ketone carbonyl groups are also characteristic of **9a**−**f**. The chemical shifts of the signals of both the exocyclic double bond and the carbonyl carbon atoms depend only on the substituent R^3 (*t*Bu, Me). For **9a**−**d**, three low-field signals (attributable to the carbon atoms attached to two nitrogen atoms) are observed in the δ = 148.7−162.8 range. As expected, five low-field signals are detected for the methoxy derivatives **9e**−**f**. For both **9e** and **9f**, two additional high-field signals arising from the π-donor effect of the oxygen atoms are observed.

Table 2. Synthesis of quinoxalines **9a**−**f**

9	R^1	R^2	R^3	Yield (%)[a]	δ[b]	δ[c]
a	H	H	CH_3	61	5.68	197.6, 161.4, 150.1, 148.7, 93.4
b	CH_3	H	CH_3	44	5.57	197.3, 162.3, 150.1, 149.4, 92.7
c	H	CH_3	CH_3	43	5.61	197.4, 162.4, 150.2, 149.6, 92.9
d	CH_3	H	$C(CH_3)_3$	80	5.83	206.0, 162.8, 150.1, 149.2, 88.8
e	OCH_3	H	CH_3	37	5.55	197.0, 162.2, 161.2, 159.2, 149.6, 149.0, 112.9, 100.8, 92.4
f	OCH_3	H	$C(CH_3)_3$	45	5.82	205.8, 163.0, 161.2, 159.2, 149.4, 149.2, 112.7, 100.7, 88.5

[a] Isolated yield. − [b] ^{1}H NMR chemical shifts of the proton of the exocyclic double bond. − [c] ^{13}C NMR chemical shifts.

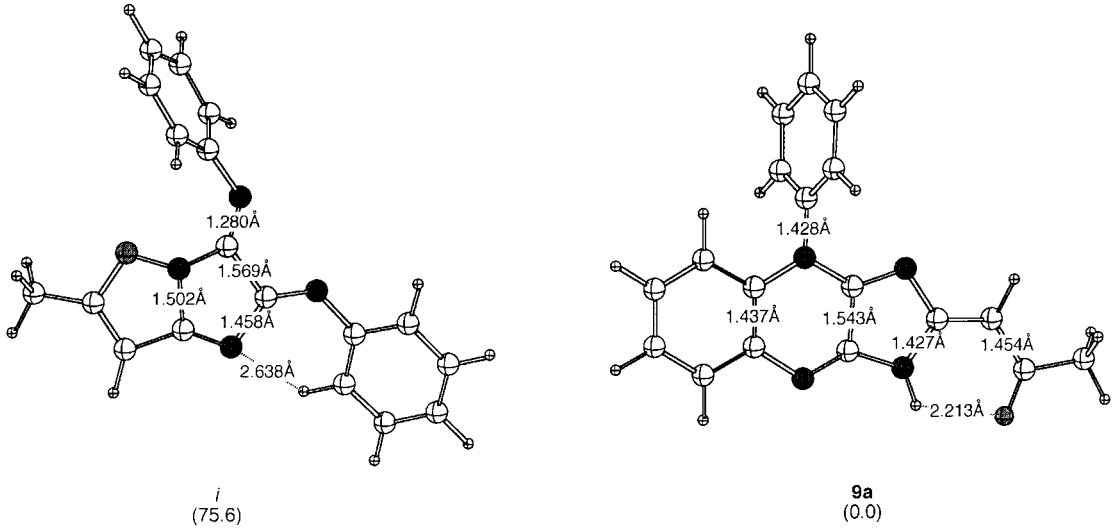


Figure 3. Domino reactions between 3-aminoisoxazoles and oxaldiimidoyl dichlorides; computed AM1 geometries of intermediate *i* and of the final product **9a**

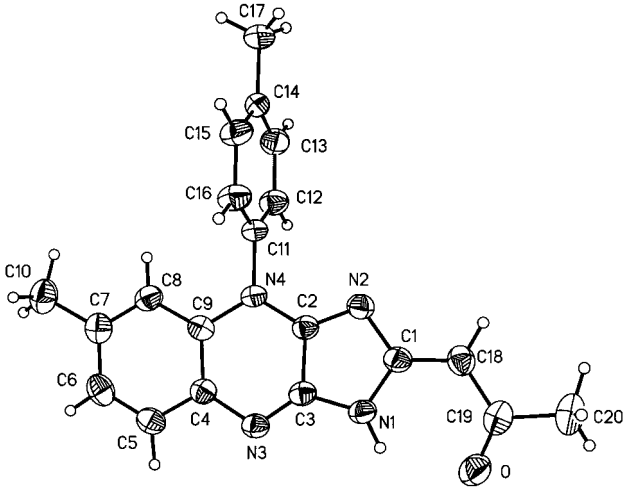
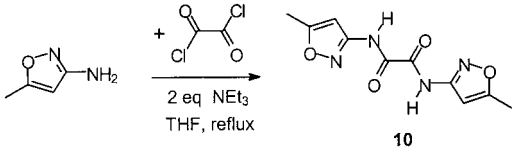


Figure 4. ORTEP plot of **9b**; 50% probability thermal ellipsoids are shown for the non-hydrogen atoms; selected bond lengths [Å] and angles [°]: O−C(19) 1.242(3), N(1)−C(3) 1.368(3), N(1)−C(1) 1.380(3), N(2)−C(1) 1.396(3), N(3)−C(3) 1.288(3), N(4)−C(2) 1.345(3), C(2)−C(3) 1.453(3), C(4)−C(5) 1.399(3), C(5)−C(6) 1.370(4), C(6)−C(7) 1.398(4); C(3)−N(1)−C(1) 108.8(2), C(2)−N(2)−C(1) 104.0(2), C(3)−N(3)−C(4)113.7(2), N(1)−C(1)−N(2)110.7(2), N(2)−C(2)−N(4) 128.6(2), N(2)−C(2)−C(3) 113.8(2), N(4)−C(2)−C(3) 117.6(2), N(3)−C(3)−N(1) 130.0(2), N(3)−C(3)−C(2) 127.4(2), N(3)−C(4)−C(5) 118.8(2), C(6)−C(5)−C(4) 121.3(3)

Treatment of 3-amino-5-methylisoxazole with oxalyl dichloride resulted in formation of the open-chain amide **10** rather than cyclization (Scheme 4). When **10** was heated to reflux in the presence of triethylamine for 96 h, only unchanged starting material was recovered.



Scheme 4. Reaction between 3-amino-5-methylisoxazole and oxalyl dichloride

Conclusions

In summary, we report new and preparatively useful cyclizations between 3-aminopyrazoles, 3-amino-1,2,4-triazole and 3-aminoisoxazoles and oxaldiimidoyl dichlorides. These reactions provide convenient and regioselective access to a variety of biologically relevant heterocycles. 2,4-Dihydro-1*H*-imidazo[4,5-*b*]quinoxalines **9** were efficiently prepared under thermodynamic control by a new anionic domino reaction.

Experimental Section

General Comments: All solvents were dried by standard methods and all reactions were carried out under an inert gas. − The oxaldiimidoyl dichlorides **2** were prepared according to literature procedures.[7] − For ^{1}H NMR and ^{13}C NMR spectra, the deuterated solvents indicated were used. − Mass spectrometric (MS) data were obtained using the electron ionization (70 eV) or the chemical ionization techniques (CI, H_2O). − For preparative scale chromatography, silica gel (60−200 mesh) was used. − Melting points are uncorrected. − Elemental analyses were performed at the microanalytical laboratories of the Universities of Hannover and Jena.

Crystal Structure Determination:[15] The intensity data for the compounds were collected with a Nonius KappaCCD diffractometer, using graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption.[16,17] The structures were solved by direct methods (SHELXS)[18] and refined by full-matrix, least-squares techniques against F_o^2 (SHELXL-97).[19] The hydrogen atoms of the structures were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically.[19] XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

Crystal Data for 4: $C_{20}H_{18}N_8$, M = 370.42 gmol^{-1}, colourless prisms, size 0.34 × 0.32 × 0.28 mm, tetragonal, space group $P4_32_12$, a = 10.766(1), b = 10.766(1), c = 16.822(2) Å, V = 1949.8(3) Å^3, T = −90 °C, Z = 4, $\rho_{calcd.}$ = 1.262 gcm^{-3}, μ(Mo-K_α) = 0.82 cm^{-1}, F(000) = 776, 5279 reflections in h (0/11), k (−11/12), l (−18/18), measured in the range 2.25° ≤ θ ≤ 23.40°, completeness θ_{max} = 97.8%, 1410 independent reflections, R_{int} = 0.101, 1354 reflections with $F_o > 4\sigma(F_o)$, 132 parameters, 0 restraints, $R1_{obs}$ = 0.057, $wR2_{obs}$ = 0.135, $R1_{all}$ = 0.091, $wR2_{all}$ = 0.197, GOOF = 1.108, Flack parameter 6(5), largest difference peak and hole: 0.141/−0.145 eÅ^{-3}.

Crystal Data for 9b: $C_{20}H_{18}N_4O$, M = 330.38 gmol^{-1}, size 0.38 × 0.20 × 0.20 mm, triclinic, space group $P\bar{1}$, a = 9.607(1), b = 9.650(1), c = 10.964(1) Å, α = 106.22(1), β = 97.20(1)°, γ = 116.66(1), V = 834.2(1) Å^3, Z = 2, $\rho_{calcd.}$ = 1.315 gcm^{-3}, μ(Mo-K_α) = 0.084 mm^{-1}, F(000) = 348, 3612 reflections in h (−10/11), k (−12/0), l (−13/13), measured in the range 2.48° ≤ θ ≤ 26.34°, 3400 independent reflections, R_{int} = 0.0233, 2619 reflections with $F_o > 4\sigma(F_o)$, 298 parameters, 0 restraints, $R1_{obs}$ = 0.0490, $wR2_{obs}$ = 0.1137, $R1_{all}$ = 0.1439, $wR2_{all}$ = 0.1588, GOOF = 0.940, largest difference peak and hole: 0.179/−0.228 eÅ^{-3}.

General Procedure for the Preparation of 2,3-Bis(arylimino)-3*H*-imidazo[1,2-*b*]pyrazoles 3: A THF solution of 3-aminopyrazole (5.0 mmol) was added to a solution of **2** (415 mg, 5.0 mmol) and Et_3N (1.4 mL, 10.0 mmol) in THF (50 mL) and the mixture was refluxed for 4 h. The precipitated Et_3NHCl was removed by filtration and the filtrate solvent was removed in vacuo. Methanol was added to the orange residue and the precipitated orange product was isolated, dried in vacuo and recrystallized from ethanol or DMF.

2,3-Bis(phenylimino)-3*H*-imidazo[1,2-*b*]pyrazole (3a): Yield 833 mg (58%) of red crystals, m.p. 168−170 °C. − ^{1}H NMR (200 MHz, [D$_7$]DMF): δ = 5.88 (d, 1 H, Hetar-CH, J = 1.7 Hz), 7.15−7.56 (m, 11 H, Ar), 10.33 (s, 1 H, NH). − ^{13}C NMR (50 MHz, [D$_7$]DMF): δ = 93.1, 120.9, 123.5, 124.7, 126.9, 129.2, 129.5, 137.5, 139.6, 145.0, 149.3, 160.3, 162.4. − IR (Nujol): $\tilde{\nu}$ = 3204, 3141, 3123 (m, ν_{NH}), 1706, 1642 (s, $\nu_{C=N}$),1590 (s), 1563 (s), 1547 (s), 1498 (s) cm^{-1}. − MS (CI, H_2O): m/z (%) = 288 (100) [M$^+$ + 1], 269 (8), 241 (7), 185 (6), 93 (13). − $C_{17}H_{13}N_5$ (287.32): C 71.07, H 4.56, N 24.37; found C 70.89, H 4.77, N 23.54%.

2,3-Bis(4-tolylimino)-3*H*-imidazo[1,2-*b*]pyrazole (3b): Yield 741 mg (47%) of red crystals, m.p. 177−179 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 2.36, 2.37 (2 × s, 2 × 3 H, Tol-CH$_3$), 5.75 (d, 1 H, Hetar-CH, J = 1.5 Hz), 7.22 (d, 4 H, Ar-CH, J = 8.2 Hz), 7.46−7.53 (m, 3 H, Ar, Hetar), 7.71 (d, 2 H, Ar-CH, J = 8.1 Hz), 8.09 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 21.0, 21.4 (Tol-CH$_3$), 93.2, 119.8, 120.2, 124.3, 129.7, 130.1, 134.7, 135.5, 136.2, 137.9, 141.2, 149.0, 159.1, 162.5. − IR (Nujol): $\tilde{\nu}$ = 3312 (w, ν_{NH}), 1691, 1639 (m, $\nu_{C=N}$), 1560 (s), 1506 (m) cm^{-1}. − MS (EI, 70 eV): m/z (%) = 315 (13) [M$^+$], 198 (22), 116 (17), 91 (100), 77 (16), 65 (47). − $C_{19}H_{17}N_5$ (315.38): C 72.36, H 5.43, N 22.21; found C 71.80, H 5.41, N 22.11.

5-Methyl-2,3-bis(4-tolylimino)-3*H*-imidazo[1,2-*b*]pyrazole (3c): Yield 1.038 g (63%) of faintly red crystals, m.p. 155−156 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 2.19 (s, 3 H, Hetar-CH$_3$), 2.35, 2.38 (2 × s, 2 × 3 H, Tol-CH$_3$), 5.61 (s, 1 H, Hetar), 7.22 (d, 4 H, Ar, J = 8.3 Hz), 7.51, 7.69 (2 × d, 2 × 2 H, Ar, J = 8.3 Hz), 8.09 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 15.2 (Hetar-CH$_3$), 21.0, 21.3 (Tol-CH$_3$), 94.2, 119.7, 120.2, 124.4, 129.7, 130.1, 134.6, 135.6, 135.9, 137.5, 141.4, 159.3, 162.9. − IR (Nujol): $\tilde{\nu}$ = 3293, 3199, 3093 (m, ν_{NH}), 1689, 1654 (s, $\nu_{C=N}$), 1631 (s), 1590 (s), 1566 (s), 1531 (s), 1504 (s) cm^{-1}. − MS (EI, 70 eV): m/z (%) = 329 (58) [M$^+$], 314 (11), 268 (38), 212 (100), 135 (17), 107 (75), 91 (53), 77 (12), 65 (20). − $C_{20}H_{19}N_5$ (329.40): C 72.93, H 5.81, N 21.26; found C 73.01, H 6.16, N 20.95.

2,3-Bis(4-methoxyphenylimino)-3*H*-imidazo[1,2-*b*]pyrazole (3d): Yield 1.198 g (69%) of faintly red crystals, m.p. 144−146 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 3.81 (s, 6 H, OCH$_3$), 5.75 (s, 1 H, Hetar), 6.94 (d, 4 H, Ar, J = 8.3 Hz), 7.50 (s, 1 H, Hetar), 7.75, 7.82 (2 × d, 2 × 2 H, Ar, J = 8.3 Hz), 8.09 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 55.9 (OCH$_3$), 92.8, 114.3, 114.8, 121.2, 127.3, 131.4, 134.7, 136.3, 148.5, 157.0, 159.1, 159.8, 162.4. − IR (Nujol): $\tilde{\nu}$ = 3340, 3285 (w, ν_{NH}), 1678, 1663 (m, $\nu_{C=N}$), 1633 (s), 1594 (s), 1562 (s), 1533 (s), 1505 (s) cm^{-1}. − MS (EI, 70 eV): m/z (%) = 347 (58) [M$^+$], 300 (17), 214 (100), 199 (40), 174 (16), 149 (18), 123 (46), 108 (42), 91 (41), 77 (11). − $C_{19}H_{17}N_5O_2$ (347.38): C 65.70, H 4.93, N 20.16; found C 66.02, H 5.13, N 19.74.

Isolation of *N*^{1},*N*^{2}-Diphenyl-*N*′^{1},*N*′^{2}-bis(1*H*-pyrazol-3-yl)ethanediimidamide (4): Compound **4** was isolated during the aqueous workup of **3a**. After filtration of **3a**, the filtrate solvent was removed in vacuo and the residue was recrystallized from hot DMF to give 460 mg (25%) of **4** as colourless prisms, m.p. 250−252 °C. − ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 5.79 (m, 2 H, Hetar), 6.57 (m, 2 H, Hetar), 6.96−7.86 (m, 10 H, Ar), 9.87 (s, 4 H, NH). − ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 114.7, 116.7, 120.0 (br), 122.4 (br), 128.4, 134.2 (br), 140.2 (br), 147.0, 150.1. − IR (Nujol): $\tilde{\nu}$ = 3133, 3080 (m, ν_{NH}), 1629 (s, $\nu_{C=N}$), 1598 (s), 1586 (s), 1498 (m), 1484 (s) cm^{-1}. − MS (EI, 70 eV): m/z (%) = 287 (14) [M$^+$ − aminopyrazole], 277 (18), 184 (36), 93 (100), 77 (14), 66 (27). − $C_{20}H_{18}N_8$ (370.42): C 64.85, H 4.90, N 30.25; found C 64.95, H 5.09, N 30.24.

Preparation of 5,6-Bis(4-tolylimino)-5*H*-imidazo[2,1-*c*][1,2,4]triazole (6) and 5,6-Bis(4-tolylimino)-6*H*-imidazo[1,2-*b*][1,2,4]triazole (7): The preparation of **6** was carried out analogously to that of heterocycles **3**. Starting with 3-amino-1,2,4-triazole (420 mg, 5.0 mmol) and oxalbis(tolylimidoyl) dichloride (**2a**) (5.0 mmol), a mixture of compounds **6** and **7** (86:14) (1.078 g, 68%) was obtained as an orange solid. The isomers were separated by repeated chromato-

graphy. − **Compound 6:** M.p. 219−221 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 2.37, 2.40 (2 × s, 2 × 3 H, Tol-CH_3), 7.03 (d, 2 H, Ar, *J* = 8.3 Hz), 7.29 (2 × d, 2 × 2 H, Ar, *J* = 7.3 Hz), 7.61 (s, 1 H, Hetar), 7.77 (d, 2 H, Ar, *J* = 8.5 Hz), 8.32 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 21.1, 21.3 (Tol-CH), 120.3, 120.7, 130.4, 131.0, 134.7, 135.1, 136.0, 137.3, 138.2, 142.6, 161.3, 170.3. − IR (Nujol): $\tilde{\nu}$ = 3247, 3216, 3153, 3112 (m, ν_{NH}), 1702, 1656 (s, $\nu_{C=N}$),1606 (s), 1547 (s), 1503 (s) cm^{-1}. − UV/Vis [λ (log ε), CH_3CN]: λ_{max} = 276 (3.73), 390 (3.97) nm. − MS (EI, 70 eV): *m*/*z* (%) = 316 (100) [M$^+$], 301 (69), 199 (68), 158 (10), 143 (8), 131 (12), 117 (12), 91 (62), 77 (11), 65 (23). − $C_{18}H_{16}N_6$ (316.37): C 68.34, H 5.10, N 26.56; found C 68.12, H 5.23, N 26.26. − **Compound 7:** M.p. 264−266 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 2.37, 2.39 (2 × s, 2 × 3 H, Tol-CH_3), 7.27 (d, 4 H, Ar, *J* = 8.3 Hz), 7.61, 7.78 (2 × d, 2 × 2 H, Ar, *J* = 8.3 Hz), 7.47 (s, 1 H, Hetar), 8.48 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 21.1, 21.5 (Tol-CH_3), 120.5, 125.3, 130.1, 130.4, 134.2, 136.2, 139.7, 140.2, 157.1, 162.3, 175.2. − IR (Nujol): $\tilde{\nu}$ = 3394, 3210, 3115 (m, ν_{NH}), 1688, 1640 (m, $\nu_{C=N}$), 1610 (w), 1593 (w), 1550 (s), 1527 (s), 1505 (s) cm^{-1}. − UV/Vis [λ (log ε), CH_3CN]: λ_{max} = 296 (3.91), 377 (4.00), 419 (4.07). − MS (EI, 70 eV): *m*/*z* (%) = 316 (84) [M$^+$], 301 (81), 199 (100), 158 (16), 131 (15), 117 (19), 91 (73), 77 (14), 65 (26). − $C_{18}H_{16}N_6$ (316.37): C 68.34, H 5.10, N 26.56; found C 68.47, H 5.00, N 26.87.

General Procedure for the Preparation of 2,4-Dihydro-1*H*-imidazo[4,5-*b*]quinoxalines 9: A toluene solution of oxaldiimidoyl dichlorides **2** (5.0 mmol), 5-alkyl-3-aminoisoxazoles **8** (5.0 mmol) and Et_3N (1.4 mL, 10.0 mmol) was refluxed for 48−96 h until **2** had been completely consumed. The precipitated Et_3NHCl was removed by filtration and the precipitate was washed carefully with hot toluene. The filtrate solvent was removed in vacuo. Methanol (2.0 mL) was added to the residue. The precipitated crude products were dried in vacuo and recrystallized from toluene to give the pure products as yellow solids.

1-(4-Phenyl-1,4-dihydro-2*H*-imidazo[4,5-*b*]quinoxalin-2-ylidene)-propan-2-one (9a): Yield 915 mg (61%) of yellow crystals, m.p. 296−299 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.16 (s, 3 H, $COCH_3$), 5.68 (s, 1 H, =CH), 6.89 (d, 1 H, Ar, *J* = 8.3 Hz), 7.24−7.45, 7.60−7.79 (2 × m, 2 × 4 H, Ar), 11.57 (s, 1 H, NH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.1 (CO*C*H$_3$), 93.4, 115.8, 125.5, 126.8, 127.9, 128.2, 130.2, 130.3, 130.6, 135.1, 136.1, 148.7, 150.1, 161.4, 197.6. − IR (Nujol): $\tilde{\nu}$ = 3248 (w, ν_{NH}), 1646 (m, $\nu_{C=O}$), 1636 (m), 1607 (m), 1516 (s) cm^{-1}. − UV/Vis (CH_3CN): λ_{max} (log ε) = 255 nm (4.11), 285 (3.85), 398 (4.43), 417 (4.61), 440 (4.43), 466 (4.36). − MS (EI, 70 eV): *m*/*z* (%) = 302 (56) [M$^+$], 287 (100), 143 (14), 137 (12), 129 (10), 77 (15). − $C_{18}H_{14}N_4O$ (302.34): C 71.51, H 4.67, N 18.53; found C 71.55, H 4.41, N 18.44.

1-[6-Methyl-4-(4-tolyl)-1,4-dihydro-2*H*-imidazo[4,5-*b*]quinoxalin-2-ylidene]propan-2-one (9b): Yield 725 mg (44%) of deep yellow crystals, m.p. 295−296 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 2.14 (s, 3 H, $COCH_3$), 2.32 (s, 3 H, Tol-CH_3), 2.53 (s, 3 H, quinoxaline-CH_3), 5.57 (s, 1 H, =CH), 6.76 (s, 1 H, quinoxaline-CH), 7.19 (d, 1 H, Ar, *J* = 8.3 Hz), 7.31, 7.49 (2 × d, 2 × 2 H, Ar, *J* = 8.2 Hz), 7.65 (d, 1 H, quinoxaline-CH, *J* = 8.3 Hz), 11.59 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 21.5, 21.7 (Ar-CH_3), 30.1 ($COCH_3$), 92.7, 116.3, 127.0, 128.0, 128.1, 130.7, 131.5, 133.2, 134.7, 138.0, 141.1, 149.4, 150.1, 162.3, 197.3. − IR (Nujol): $\tilde{\nu}$ = 3285 (m, ν_{NH}), 1645 (s, $\nu_{C=O}$), 1609 (s), 1598 (s), 1518 (s), 1511 (s), 1492 (s) cm^{-1}. − UV/Vis (CH_3CN): λ_{max} (log ε) = 259 nm (4.17), 289 (3.87), 389 (4.48), 420 (4.70), 443 (4.74), 470 (4.49). − MS (CI, H_2O): *m*/*z* (%) = 331 (100) [M$^+$ + 1], 315 (8), 99 (51), 93 (64). − $C_{20}H_{18}N_4O$ (330.39): C 72.71, H 5.49, N 16.96; found C 72.65, H 5.72, N 16.35.

1-[8-Methyl-4-(2-tolyl)-1,4-dihydro-2*H*-imidazo[4,5-*b*]quinoxalin-2-ylidene]propan-2-one (9c): Yield 713 mg (43%) of yellow needles, m.p. 244−246 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 2.02, 2.16 (2 × s, 2 × 3 H, Ar-CH_3), 2.91 (s, 3 H, $COCH_3$), 5.61 (s, 1 H, =CH), 6.63 (d, 1 H, quinoxaline-CH, *J* = 8.2 Hz), 7.13−7.31, 7.43−7.60 (2 × m, 6 H, Ar, Hetar), 11.66 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 17.6, 18.1 (Ar-CH_3), 30.2 ($COCH_3$), 92.9, 113.8, 121.9, 126.2, 126.8, 127.2, 128.5, 130.1, 132.4, 135.3, 136.4, 137.2, 149.6, 150.2, 162.4, 197.4. − IR (Nujol): $\tilde{\nu}$ = 3285 (m, ν_{NH}), 1652 (s, $\nu_{C=O}$), 1637 (m), 1608 (m), 1597 (m), 1530 (s) cm^{-1}. − UV/Vis (CH_3CN): λ_{max} (log ε) = 259 nm (3.77), 278 (3.63), 398 (4.01), 420 (4.21), 443 (4.25), 470 (3.98). − MS (EI, 70 eV): *m*/*z* (%) = 330 (46) [M$^+$], 315 (100), 151 (11), 107 (8), 91 (17), 65 (9). − $C_{20}H_{18}N_4O$ (330.39): C 72.71, H 5.49, N 16.96; found C 72.54, H 5.56, N 16.87.

3,3-Dimethyl-1-[6-methyl-4-(4-tolyl)-1,4-dihydro-2*H*-imidazo[4,5-*b*]quinoxalin-2-ylidene]butan-2-one (9d): Yield 1.488 g (80%) of yellow crystals, m.p. 328−330 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 1.16 [s, 9 H, C(CH_3)$_3$], 2.31 (s, 3 H, Tol-CH_3), 2.52 (s, 3 H, quinoxaline-CH_3), 5.83 (s, 1 H, =CH), 6.75 (s, 1 H, quinoxaline-CH), 7.16 (d, 1 H, quinoxaline-CH, *J* = 8.2 Hz), 7.32, 7.49 (2 × d, 2 × 2 H, Ar, *J* = 8.3 Hz), 7.62 (d, 1 H, quinoxaline-CH, *J* = 8.2 Hz), 11.48 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 21.5, 21.7 (Tol-CH_3, Hetar-CH_3), 27.6 [C(*C*H$_3$)$_3$], 42.8 [*C*(CH$_3$)$_3$], 88.8, 116.2, 126.8, 128.0, 128.1, 130.7, 131.4, 133.2, 134.6, 137.9, 141.0, 149.2, 150.1, 162.8, 206.0. − IR (Nujol): $\tilde{\nu}$ = 3296 (m, ν_{NH}), 1649 (s, $\nu_{C=O}$), 1612 (s), 1604 (s), 1586 (m), 1558 (s), 1531 (s), 1511 (s), 1496 (s) cm^{-1}. − UV/Vis (CH_3CN): λ_{max} (log ε) = 260 nm (4.23), 288 (3.96), 398 (4.56), 421 (4.76), 445 (4.80), 471 (4.54). − MS (EI, 70 eV): *m*/*z* (%) = 372 (13) [M$^+$], 315 (100), 288 (5), 91 (8), 28 (12). − $C_{23}H_{24}N_4O$ (372.47): C 74.17, H 6.49, N 15.04; found C 74.19, H 6.61, N 14.77.

1-[6-Methoxy-4-(4-methoxyphenyl)-1,4-dihydro-2*H*-imidazo[4,5-*b*]quinoxalin-2-ylidene]propan-2-one (9e): Yield 668 mg (37%) of yellow crystals, m.p. 266−268 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 2.13 (s, 3 H, $COCH_3$), 3.70, 3.93 (2 × s, 2 × 3 H, OCH_3), 5.55 (s, 1 H, =CH), 6.44 (s, 1 H, quinoxaline-CH), 6.96 (dd, 1 H, quinoxaline-CH, *J* = 8.9 Hz), 7.17, 7.36 (2 × d, 2 × 2 H, Ar, *J* = 6.8 Hz), 7.68 (d, 1 H, quinoxaline-CH, *J* = 8.9 Hz), 11.53 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 30.0 (CO*C*H$_3$), 56.0, 56.1 (OCH_3), 92.4, 100.8, 112.9, 116.1, 128.2, 129.3, 129.4, 131.1, 132.2, 149.0, 149.6, 159.2, 161.2, 162.2, 197.0. − IR (Nujol): $\tilde{\nu}$ = 3175 (m, ν_{NH}), 1642 (s), 1607 (m), 1588 (m), 1562 (s), 1534 (s), 1514 (s), 1494 (s) cm^{-1}. − UV/Vis (CH_3CN): λ_{max} (log ε) = 264 nm (4.08), 295 (3.78), 400 (4.34), 425 (4.60), 448 (4.67), 474 (4.45). − MS (CI, H_2O): *m*/*z* (%) = 363 (100) [M$^+$ + 1], 347 (8), 257 (6), 167 (3), 93 (17). − $C_{20}H_{18}N_4O_3$ (362.39): C 66.29, H 5.01, N 15.46; found C 66.65, H 5.24, N 15.25.

1-[6-Methoxy-4-(4-methoxyphenyl)-1,4-dihydro-2*H*-imidazo[4,5-*b*]quinoxalin-2-ylidene]-3,3-dimethylbutan-2-one (9f): Yield 912 mg (45%) of deep yellow crystals, m.p. 278−280 °C. − ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 1.16 [s, 9 H, C(CH_3)$_3$], 3.70, 3.92 (2 × s, 2 × 3 H, OCH_3), 5.82 (s, 1 H, =CH), 6.43 (d, 1 H, quinoxaline-CH, ^4J = 2.6 Hz), 6.95 (dd, 1 H, quinoxaline-CH, ^4J = 2.6 Hz, ^3J = 8.9 Hz), 7.16, 7.36 (2 × d, 4 H, Ar, *J* = 8.9 Hz), 7.66 (d, 1 H, quinoxaline-CH, *J* = 8.9 Hz), 11.47 (s, 1 H, NH). − ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 27.7 [C(*C*H$_3$)$_3$], 42.7 [*C*(CH$_3$)$_3$], 56.1 (OCH_3), 88.5, 100.7, 112.7, 116.1, 128.2, 129.3, 129.4, 131.1, 132.2, 149.2, 149.4, 159.2, 161.2, 163.0, 205.8. − IR (Nujol): $\tilde{\nu}$ = 3279

(w, ν_{NH}), 1645 (s, $\nu_{C=O}$), 1607 (m), 1599 (s), 1576 (s), 1557 (s), 1530 (s), 1512 (s), 1500 (s) cm^{-1}. – UV/Vis (CH_3CN): λ_{max} (log ε) = 265 nm (4.05), 288 (3.72), 399 (4.37), 427 (4.58), 449 (4.64), 476 (4.40). – MS (CI, H_2O): *m/z* (%) = 405 (100) [M^+ + 1], 347 (13), 141 (5), 93 (27). – $C_{23}H_{24}N_4O_3$ (404.47): C 68.30, H 5.98, N 13.85; found C 67.71, H 6.17, N 13.58.

Preparation of *N,N′*-Bis(5-methylisoxazol-3-yl)ethanediamide (10): A toluene solution (50 mL) of 3-amino-5-methylisoxazole (1.0 g, 10.0 mmol) and Et_3N (1.4 mL, 10.0 mmol) was added at 0 °C to a toluene solution (50 mL) of oxalyl dichloride (0.43 mL, 5.0 mmol). The temperature of the reaction mixture was allowed to rise to 20 °C. The colourless precipitate was filtered off, washed with water and MeOH and recrystallized from DMF to give 1.202 g of colourless crystals (96%), m.p. 308–310 °C. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.43 (s, 6 H, Hetar-CH_3), 7.24 (s, 2 H, Hetar), 9.58 (br, 2 H, NH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.3 (Hetar-CH_3), 96.0, 156.5, 157.8, 169.4. – IR (Nujol): $\tilde{\nu}$ = 3313, 3146 (s, ν_{NH}), 1691 (s, $\nu_{C=O}$), 1615 (s), 1540 (s) cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 250 (9) [M^+], 125 (100), 98 (96), 83 (7), 70 (12), 55 (20), 43 (32). – $C_{10}H_{10}N_4O_4$ (250.21): C 48.00, H 4.03, N 22.39; found C 48.07, H 4.02, N 22.47.

Computational Methods: Details pertaining to the computational methods are given in the preceding paper.[6] Geometries were fully optimized at the semiempirical AM1 level of theory, using analytical gradients as implemented in the Gaussian 98 program package. Harmonic vibrational frequencies were computed to ascertain the nature of all stationary points; the number of the imaginary modes is 0 for minima and 1 for the transition structures. All computed energies and geometries are available as supplementary materials from the authors upon request.

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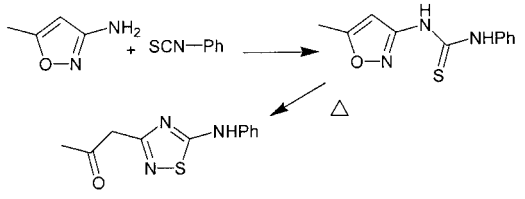

[15] Further details of the crystal structure investigations are available on request from the Cambridge Crystallographic Data Centre CCDC (12 Union Road, Cambridge CB2 1EZ, UK), quoting the depository numbers CCDC-132367 (**9b**), and -140091 (**4**), the names of the authors, and the journal citation.

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