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The Synthesis of 6-Amidino-2-oxopurine Revisited: New Evidence for the Reaction Mechanism

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Treatment of *N*-aryl- or *N*-alkyl-5-amino-4-(cyanoformimidoyl)-1*H*-imidazoles **1** with benzoyl or ethoxycarbonyl isocyanates resulted in the formation of 5-amino-4-[*N*-benzoyl- or *N*-(ethoxycarbonyl)carbamoylcyanoformimidoyl]-1*H*-imidazoles **2**. In the presence of catalytic amounts of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), these compounds cyclized to give the 5′-amino-5-imino-4,4′-bi-1*H*-imidazol-2(5*H*)-ones **3**. Compounds **3** efficiently rearrange to yield 6-amidino-2-oxopurines **5** in ethanol or DMF solution. The formation of purines **5** both from imidazoles **2** and from bi-imidazoles **3** was followed by ^{1}H NMR, allowing a deeper understanding of the reaction mechanism. The rearrangements are acid-catalysed (trifluoroacetic acid), but the use of one equivalent of acid produced different products, identified as the bi-imidazoles **8**.

Introduction

Purine-based compounds display an impressively wide range of biological activities and find potential for application mainly as therapeutic agents.[1] The potencies and selectivities of these compounds are intimately related to the position and nature of the substituents on the rings. The synthesis of new purine derivatives and the development of new versatile synthetic methods that will allow the preparation of diverse libraries of these compounds is a highly important topic.[2]

The biological importance of puromycin and of a number of *N*-substituted or *N*,*N*-disubstituted derivatives is documented in previous publications.[3] From structure/activity relationship studies, it has been established that, in some cases, a basic group in the 6-position is essential for activity.[4] Unlike in the cases of adenine and adenine derivatives, which have been extensively studied, only a few reports on the synthesis of purines possessing a strongly basic carboxamidino substituent at the 6-position are available. The formation of these compounds has been claimed to occur through nucleophilic attack by a primary or secondary amine on a 6-cyanopurine,[5] or through addition of ammonium chloride to an imidate intermediate, generated by treatment of a 6-cyanopurine with catalytic amounts of sodium methoxide in methanol.[6]

A limited number of publications on the synthesis of 4,4′-biimidazoles are available. These compounds have been prepared by palladium-catalysed coupling of *N*-protected 4-iodoimidazoles[7] or from an *N*-protected 4-substituted imidazole and an appropriate spacer incorporated between the two heterocyclic units, in two to five steps.[8] The prepared 4,4′-biimidazole derivatives have been used as bridging ligands for two-dimensional transition metal complexes[7b] or as building blocks for supramolecular assemblies.[8a,8b,9] Their use as molecular probes for peripheral sites of the zinc endopeptidase of botulinum neurotoxin serotype A, a potential bioterror agent for which there is no chemical antidote, has also been reported.[8c]

Recent work in our group on reactions between tosyl isocyanate and *N*-aryl- or *N*-alkyl-5-amino-4-(cyanoformimidoyl)-1*H*-imidazoles **1** showed that this is a mild and efficient method for the synthesis of 6-amidino-2-oxopurines **5** (R^1 = alkyl or aryl, R^2 = tosyl).[10] The synthetic pathway postulated for this reaction (Scheme 1) regarded intermediates **2** and **3** as plausible precursors of purines **5**, the only compounds isolated under the experimental conditions used (acetonitrile at 0 to –15 °C). In subsequent studies, imidazoles **1** (R^1 = alkyl or aryl) were treated with alkyl, aryl and allyl isocyanates and in this case it was possible to isolate and characterize the ureas **2**.[11] Addition of DBU to suspensions of compounds **2** in acetonitrile proved to be an efficient synthetic method leading to 4,4′-bi-imidazolones **3**. The formation of purines **5** requires ring-opening of the imidazolone units in compounds **3**, giving rise to reactive isocyanate functions (**4**), the precursors of 2-oxopurines **5**. Attempts to generate purines **5** from bi-imidazoles **3** (R^2 = alkyl, aryl or allyl) failed in all these cases.[11]

The results suggest that this type of rearrangement can only occur when R^2 is an electron-withdrawing group. In order to understand the circumstances that enable the for-

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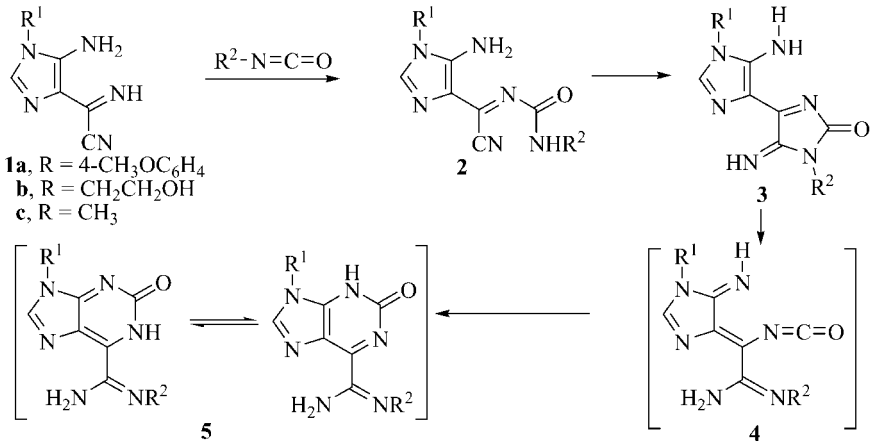


Compound	R^1	R^2	Reagents and reaction conditions	Yield (%)
2a	4-$MeOC_6H_4$	COOEt	**1a** + R^2NCO (1.9 equiv.), acetonitrile, N_2, 20 min (0 °C)	100
2b	CH_2CH_2OH	COOEt	**1b** + R^2NCO (1.4 equiv.), acetonitrile, N_2, 2 h (–4 °C)	73
2c	4-$MeOC_6H_4$	COPh	**1a** + R^2NCO (1.5 equiv.), acetonitrile, N_2, 3 h (–15 °C)	91
2d[a]	CH_2CH_2OR'	COPh	**1b** + R^2NCO (2.5 equiv.), acetonitrile, N_2, 7 h (4 °C)	95
2e	CH_3	COPh	**1c** + R^2NCO (1.5 equiv.), acetonitrile, N_2, 30 min (–15 °C)	70[b]
2f	CH_3	Ts	**1c** + R^2NCO (2.0 equiv.), acetonitrile, N_2, 45 min (–4 °C)	12[c]
			1c + R^2NCO (2.0 equiv.), acetonitrile, N_2, 15 min (–15 °C)	39[d]
3a	4-$MeOC_6H_4$	COOEt	**2a** + DBU (0.08 equiv.), acetonitrile, 5 min (r.t.)	88
3b	CH_2CH_2OH	COOEt	**2b** + DBU (0.2 equiv.), acetonitrile, 15 min (r.t.)	82
3c	4-$MeOC_6H_4$	COPh	**2c** + DBU (0.05 equiv.), acetonitrile, 2,5 h (r.t.)	82
3e	CH_3	COPh	**2e** + DBU (0.01 equiv.), acetonitrile, 15 min (0 °C) **2a** + NEt_3 (1 equiv.), acetonitrile, 15 min (r.t.)	88 90
5a	4-$MeOC_6H_4$	COOEt	**3a**, DMF, 3 days (r.t.) **3a**, ethanol, 7 days (r.t.) **2a**, DMF, 18 h (4 °C)	89 57 84
5b	CH_2CH_2OH	COOEt	**2b**, DMF, 1 day (r.t.) **2b**, ethanol, 3 days (r.t.)	76 48
5c	4-$MeOC_6H_4$	COPh	**2c**, ethanol, 6 days (r.t.) **2c**, ethanol, 25 min (reflux) **2c**, DMF, 7 h (0 °C)	94 8 84
5d[a]	CH_2CH_2OR'	COPh	**2d**, DMF, 18 h (r.t.) **2d**, ethanol, 4 days (r.t.) **2d**, ethanol, 90 min (reflux) **2d**, ethanol, 14 days (10 °C)	13 60 53 88
5e	CH_3	COPh	**2e**, ethanol, 6 days (r.t.) **3e**, ethanol, 12 days (r.t.) **2e**, TFA (cat), acetonitrile, 20 min (r.t.)	88 86 92

[a] R' = CONHPh. [b] **5e** (4%) was also isolated. [c] **5f** (79%) was also isolated. [d] **5f** (52%) was also isolated.

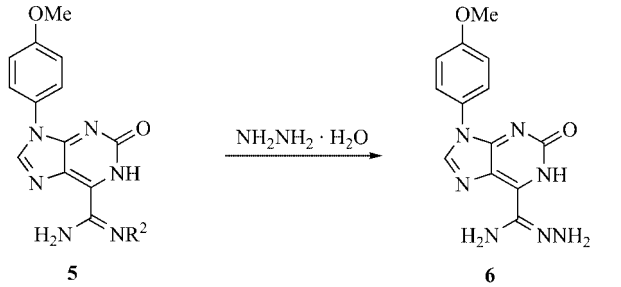
Scheme 1.

mation of a 6-amidino-2-oxopurine **5** or the isolation of a stable 4,4′-bi-1*H*-imidazol-2(5*H*)-one **3**, acyl isocyanates were treated with *N*-alkyl- and *N*-aryl-5-amino-4-(cyanoformimidoyl)imidazoles **1**.

Results and Discussion

The reactions between imidazoles **1** and benzoyl or ethoxycarbonyl isocyanates (Scheme 2) were carried out under nitrogen at low temperature (0 to –15 °C) in the presence of excess isocyanate (1.4 to 2.5 molar equivalents) and in acetonitrile as solvent. Under these experimental conditions, fast reactions occur (20 min to 7 h) and ureas **2** precipitate from the reaction mixtures as yellow-orange solids, isolated in very good yields. The reaction between imidazole **1c** (R^1 = Me) and tosyl isocyanate was also carried out at –4 °C, giving a poor isolated yield of **2f** (12%). In this case the major product (79%) was purine **5f**, rapidly formed in

the reaction mixture by further reaction of **2f**. A reduction of the temperature to –15 °C and stirring of the reaction mixture for 10 min resulted in the isolation of an orange solid identified as **2f** (39%) from its elemental analysis and IR spectrum. As soon as the solid is dissolved in [D_6]-DMSO, the ^{1}H NMR spectrum indicates that imidazole **2f** and bi-imidazolone **3f** are present as an equilibrium mixture in approximately 1:1 ratio. Purine **5f** is also identified in the spectrum, as a result of the further reaction of **3f**. The second crop is again purine **5f** (52%).



5 **6**

Compound	R^2	equiv. ($NH_2NH_2 \cdot H_2O$)	Reaction Conditions	Yield of **6** (%)
5a	COOEt	3.1	ethanol, 18 h (r.t.)	100
5c	COPh	2.0	ethanol, 2 days (r.t.)	98
5g	Tos	2.6	acetonitrile, 3 days (r.t.)	79

Scheme 2.

Compounds **2** usually show a very weak band in the IR spectrum in the 2222–2234 cm^{-1} region, assigned to the stretching vibration of the cyano group. This band was absent, however, in the IR spectrum of imidazole **2e**, but the presence of the cyano group was confirmed by ^{13}C NMR, as a weak band at δ = 112.7 ppm. For the other imidazoles **2**, the cyano group was identified in the same spectral region (δ = 112.0–112.7 ppm). The carbonyl stretching vibration in the IR spectrum occurred over a range from 1759 to 1712 cm^{-1}, which may be due to tautomerism in the β-dicarbonyl unit, occurring to a different extent for each compound and each solvent system used for recrystallization. The tautomeric equilibrium is clearly affecting the imidazole carbon atoms in compound **2d**, as all the signals in the ^{13}C NMR spectrum are broad ([D_6]DMSO solution). In the ^{1}H NMR spectra, the chemical shifts for the urea N–H groups in imidazoles **2a**–**f** (δ = 10.35–11.60 ppm) and for the imine N–H moieties in 4,4′-biimidazoles **3a**–**f** (δ = 10.40–10.75 ppm) are high, as would be expected for an acidic proton. Table 1 shows the chemical shifts for these protons ([D_6]DMSO solution) and also includes previously reported data for analogous compounds.[10,11]

The figures indicate that the substituent R^1 (alkyl or aryl) in the 1-position of the imidazole ring does not substantially affect the chemical shift of the N–H proton. This value gradually increases as R^2 changes, though, in the order Et, Bu < allyl < CH_2Ph < Ph < 4-$CF_3C_6H_5$ < COOEt < COPh. The Hammett constants (σI and σR) for these substituents were calculated[12] in order to study the relationship between these values and the experimentally measured N–H chemical shifts. The Hammett plot for the δN–H systems in compounds **2** exhibited poor correlation both with σR (R^2 = 0.757) and with σI (R^2 = 0.855). Slightly better results were registered in the Hammett plots for the N–H chemical shifts of compounds **3** and σR (R^2 = 0.890) or σI (R^2 = 0.815). We can envisage a slight predominance of the inductive effect of the substituent R^2 over the resonance effect in compounds **2** and the opposite situation in compounds **3**. Nevertheless, the possibility of tautomeric equilibria and especially of intramolecular hydrogen bonding may be affecting the acidities of the N–H protons and the corresponding chemical shift values.

Addition of base (0.02 to 0.25 molar equivalents of DBU) to suspensions of imidazoles **2** in acetonitrile results in the formation of stable anions, followed by rapid intramolecular cyclization to give 4,4′-bi-1*H*-imidazol-2(5*H*)-ones **3**, which precipitate from the reaction mixtures. The reactions occur at room temperature or in an ice bath. Triethylamine (1 molar equivalent) was also used for the cycli-

Table 1. ^{1}H NMR chemical shifts for the acidic N–H systems of compounds **2** and **3** in [D_6]DMSO solutions.

R^1	R^2	δ N–H for compounds **2**	δ N–H for compounds **3**	σR	σI
$(CH_2)_2OCONHEt$	Et	7.88	[a]	–0.14	–0.01
4-$CH_3OC_6H_4$	Et	7.99	9.60	–0.14	–0.01
4-$CH_3OC_6H_4$	*n*Bu	7.98	9.76	–0.15	–0.01
CH_2CH_2OH	allyl	8.01	9.73	–0.14	0.02
4-$CH_3OC_6H_4$	allyl	8.17	9.78	–0.14	0.02
4-$CH_3OC_6H_4$	CH_2Ph	8.35	9.80	–0.13	0.00
CH_2CH_2OH	CH_2Ph	8.35	9.77	–0.13	0.00
CH_2CH_2OH	Ph	10.00	10.06	–0.11	0.12
4-$CH_3OC_6H_4$	Ph	10.18	10.08	–0.11	0.12
CH_2CH_2OH	4-$CF_3C_6H_4$	10.27	10.21	0.01	0.19
4-$CH_3OC_6H_4$	4-$CF_3C_6H_4$	10.43	10.23	0.01	0.19
CH_2CH_2OH	COOEt	10.35 (**2b**)	10.75 (**3b**)	0.11	0.30
4-$CH_3OC_6H_4$	COOEt	10.50 (**2a**)	10.80 (**3a**)	0.11	0.30
$(CH_2)_2OCONHCOPh$	COPh	10.80 (**2d**)	[b] (**3d**)	0.11	0.31
Me	COPh	10.80 (**2e**)	10.44 (**3e**)	0.11	0.31
4-$CH_3OC_6H_4$	COPh	10.90 (**2c**)	10.40 (**3c**)	0.11	0.31
Me	Ts	11.60 (**2f**)	10.60 (**3f**)[c]	0.11	0.54

[a] Not prepared. [b] Not isolated. [c] Detected in the reaction mixture.

zation of **2e** ($R^1 = CH_3$, $R^2 = COPh$) and the reaction was equally fast at room temperature, providing the product **3e** in 90% isolated yield.

The cyclization of compound **2f** ($R^1 = CH_3$, $R^2 = Ts$) is exceptionally fast, even in the absence of base. It occurs spontaneously in the reaction mixture, the only stable compound being purine **5f**, which can be isolated in a good yield.

The further reactions of compounds **3a** and **3e** to give the corresponding purines **5** were carried out at room temperature in ethanol or DMF. The reactions took 3–12 d, mainly due to the insolubility of the bi-imidazoles **3** in these solvents. Faster and more efficient reactions occurred when solutions of imidazoles **2** in large volumes of DMF or ethanol were stirred at room temperature, as the bi-imidazoles **3** were kept in solution. The IR spectra of bi-imidazoles **3** indicate that the cyano groups are no longer present, whilst two intense bands in the 1750–1740 cm^{-1} and 1710–1670 cm^{-1} regions can be assigned to the carbonyl stretching vibrations. All compounds give poor ^{13}C NMR spectra due to their low solubilities in [D_6]DMSO.

The 6-amidinopurines **5a**, **5c** and **5g** were treated with hydrazine hydrate in either ethanol or acetonitrile as solvents (Scheme 2). Reactions occurred at room temperature, the amidine functions all being transformed into amidrazone substituents, to afford purine **6**, isolated as yellow solid in excellent yields. This result supports the structure assigned to the parent compound **5**.

In order to understand the mechanism for purine formation both from the ureas **2** and from the bi-imidazoles **3**, the reaction behaviour of these compounds was followed by ^1H NMR in [D_6]DMSO solution.

NMR Study of the Evolution of Imidazoles 2 and 3

A ^1H NMR study on the formation of purines **5** from either **2** or **3** was carried out, the reactions being monitored by measurement of the disappearance of the proton signals of the imidazole rings in compounds **2** (δ = 7.61 for **2a**, δ = 7.49 for **2b**, δ = 7.55 ppm for **2e**) and **3** (δ = 7.85 for **3a**, δ = 7.64 for **3b**, δ = 7.67 ppm for **3e**) and the appearance of the proton signals of the heterocycles **5** (δ = 8.71 for **5a**, δ = 8.41 for **5b**, δ = 8.44 ppm for **5e**). Compound **8** was monitored by the signal at δ = 7.59 ppm, attributed to the imidazole proton.

The formation of purine **5a** from either **2a** or **3a** (Figure 1) indicates that the reaction is fast. When bi-imidazole **3a** was used as the starting material, the concentration of purine **5a** had reached 50% after 10–15 min at 20 °C. When the reaction was carried out from imidazole **2a**, the same concentration of purine was registered after 15–20 min. In both cases, a rapid equilibrium between **3a** and **2a** is established in solution, resulting in similar molar ratios of these compounds (2.1–2.5), with **3a** always present as the major component.

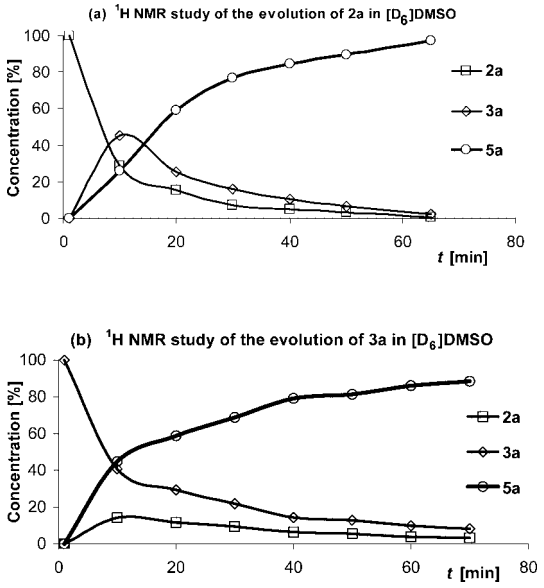


Figure 1. a) ^1H NMR study of the reaction behaviour of imidazole **2a** (□) in [D_6]DMSO solution (4 mg in 700 μL) at 20 °C. Other compounds detected in solution: bi-imidazole **3a** (✧) and purine **5a** (○). b) ^1H NMR study of the reaction behaviour of bi-imidazole **3a** (✧) in [D_6]DMSO solution (4 mg in 700 μL) at 20 °C. Other compounds detected in solution: imidazole **2a** (□) and purine **5a** (○).

A similar situation was identified when the reaction behaviour of **2e** or **3e** was followed by ^1H NMR (Figure 2). In both cases an equilibrium mixture was rapidly formed, in which only compounds **2e**, **3e** and **5e** could be identified. The concentration of approximately 50% of purine **5e** had been reached after 70 min (from **2e**) or 40 min (from **3e**), at 20 °C.

^1H NMR studies carried out on the reaction behaviour of **2b** and **3b** indicated that the two compounds follow a similar pattern (Figure 3). When the ^1H NMR spectrum of a solution of 2 mg of **3b** in [D_6]DMSO (600 μL) was measured at regular intervals, four different compounds were identified as the only products after 10 min at 20 °C. Compounds **2b**, **3b** and **5b** had been isolated and characterized previously, allowing a clear identification of their presence in solution.

From the set of peaks corresponding to the fourth compound, it was possible to identify an imidazole C–H (δ = 7.54 ppm), one N–H group (δ = 10.45 ppm) and a broad signal at δ = 9.7 ppm integrating for two protons and assigned to an NH_2 group. This compound could never be isolated or characterized by other methods and was tentatively identified as having structure **7** (Scheme 3).

The concentrations of compound **7** and of **2b** decreases in a similar way with time, suggesting that they both exist in equilibrium with **3b**. The formation of purine **5b** from **3b** continuously displaces this equilibrium, resulting in the purine being the only product in solution after less than one day. The addition of a catalytic amount of trifluoroacetic acid (TFA) to the reaction mixture (2 mg of **3b** in 600 μL of [D_6]DMSO) does not affect the reaction mecha-

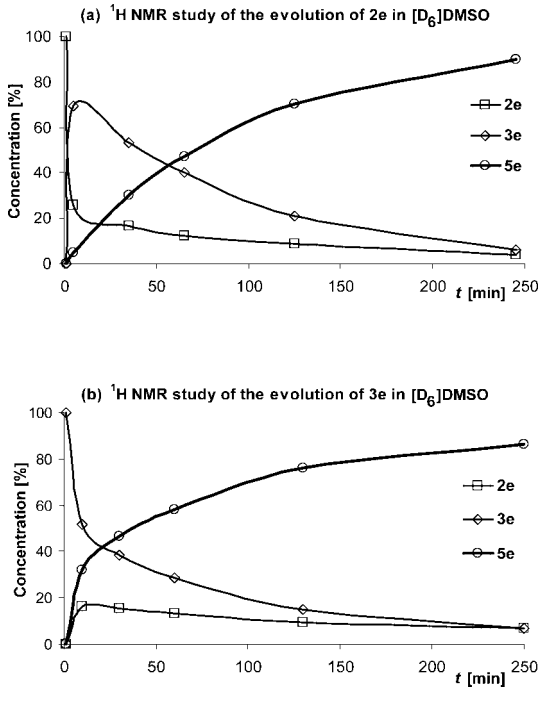


Figure 2. a) ^{1}H NMR study of the reaction behaviour of imidazole **2e** (□) in [D$_6$]DMSO solution (2 mg in 600 μL) at 20 °C. Other compounds detected in solution: bi-imidazole **3e** (✧) and purine **5e** (○). b) ^{1}H NMR study of the reaction behaviour of bi-imidazole **3e** (✧) in [D$_6$]DMSO solution (2 mg in 600 μL) at 20 °C. Other compounds detected in solution: imidazole **2e** (□) and purine **5e** (○).

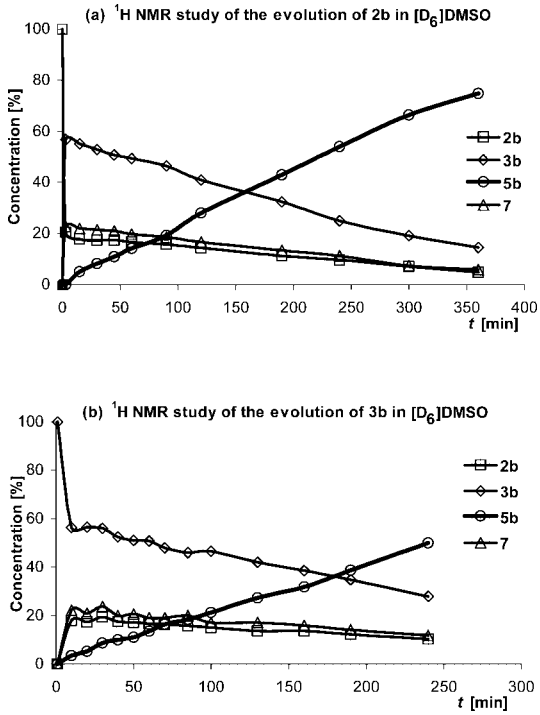


Figure 3. a) ^{1}H NMR study of the reaction behaviour of imidazole **2b** (□) in [D$_6$]DMSO solution (4 mg in 700 μL) at 20 °C. Other compounds detected in solution: bi-imidazole **3b** (✧), purine **5b** (○) and an intermediate compound with the assigned structure **7** (Δ). b) ^{1}H NMR study of the reaction behaviour of bi-imidazole **3b** (✧) in [D$_6$]DMSO solution (2 mg in 600 μL) at 20 °C. Other compounds detected in solution: imidazole **2b** (□), purine **5b** (○) and an intermediate compound with the assigned structure **7** (Δ).

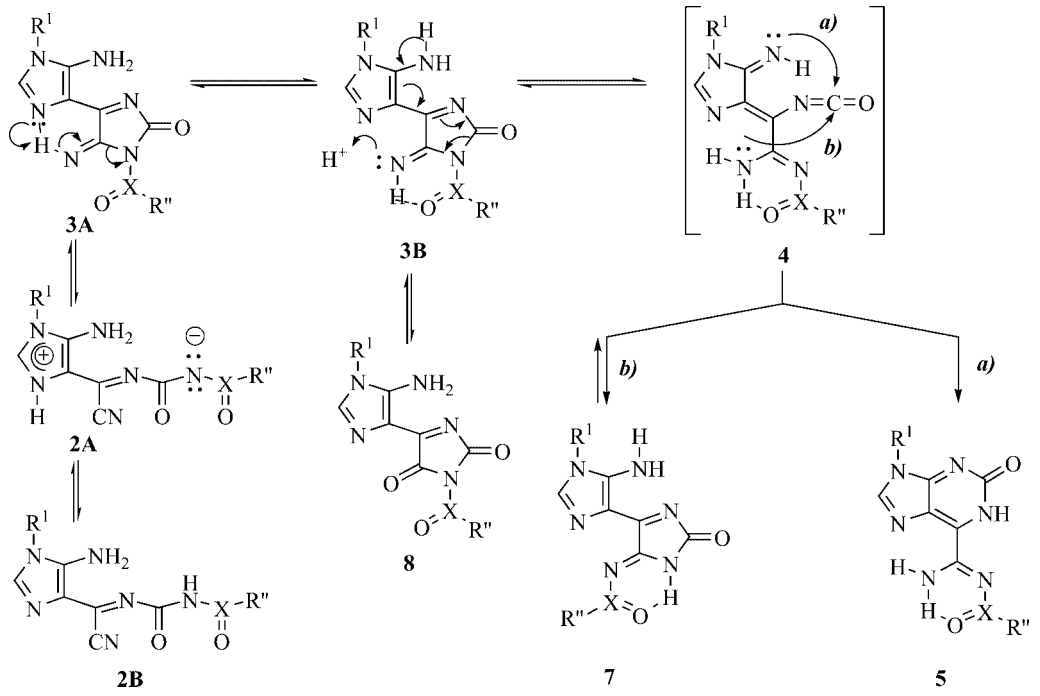
nism but does slightly enhance the rate of reaction (Figure 4, a). The concentration of purine **5b** has reached 50% after ca. 4 h at 20 °C in the absence of acid, and after ca. 3 h with acid catalysis.

The reaction behaviour of **3b** in the presence of one equivalent of TFA was also followed by ^{1}H NMR (Figure 4, b). Compound **3b** was consumed rapidly, and only a trace amount was present in solution after one hour at room temperature. Structure **3b** both reverted back to imidazole **2b** (ca. 15%) and transformed into the purine **5b** (ca. 20%) and into a new compound identified as **8** (ca. 65%), with simultaneous elimination of ammonia (the ammonium salt was identified in the spectrum as a triplet at δ = 7.10 ppm, J = 51 Hz). After 3 d at 18 °C, a very small amount of imidazole **2b** was detectable in the spectrum. Compounds **8** and **5b** were present in a 5.5:2 ratio, together with minor products probably arising from degradation processes.

Compound **8** was prepared in a separate experiment, when a suspension of **3b** in DMSO, was combined with one equivalent of trifluoroacetic acid and the mixture was stirred at room temperature for 5 hours and kept for 2 d at –18 °C. An orange solid was isolated and identified as **8** (66%) from its elemental analysis and spectroscopic data. The signal for the acidic N–H system is no longer present in the ^{1}H NMR spectrum but the NH_2 group appears as a singlet at δ = 8.56 ppm. The chemical shift of the heterocyclic C–H (δ = 7.59 ppm) clearly indicates that it is part of an imidazole structure. The IR spectrum shows the presence of three carbonyl groups, with stretching vibrations at 1781, 1745 and 1698 cm^{-1}. This observation is confirmed by ^{13}C NMR, with signals at δ = 161.0, 159.5 and 148.4 ppm.

General Mechanistic Discussion

The considerable amounts of compounds **2** detected when compounds **3** are dissolved in [D$_6$]DMSO (see parts b in Figures 1, 2 and 3) indicate that the imidazolone rings can open across two different C–N bonds. Either the imidazoles **2** are regenerated or an isocyanate function is formed and ultimately cyclizes with the 5-amino group to afford purines **5** (Scheme 3). The irreversible formation of purines **5** continuously displaces this equilibrium, and no other products were detected in solution when the reactions were carried out from **2a**, **2e**, **3a** or **3e**. The further reaction to afford 6-amidino-2-oxopurines **5** only occurs when the substituent R^2 on the bi-imidazole **3** incorporates a carbonyl or a sulfonyl group. When compound **3** (R^2 = 4-CF$_3$C$_6$H$_4$) (2 mg) was dissolved in [D$_6$]DMSO (600 μL) with a catalytic amount of trifluoroacetic acid, no transformations had occurred after 8 d at 20 °C. This result indicates that the substituent R^2 plays an important role in the ring-opening process that affords purine **5**. A possible explanation for the ring-opening of compounds **3a**–**f** might be that, in this case, two stable hydrogen bonds can be established, one of them



Scheme 3.

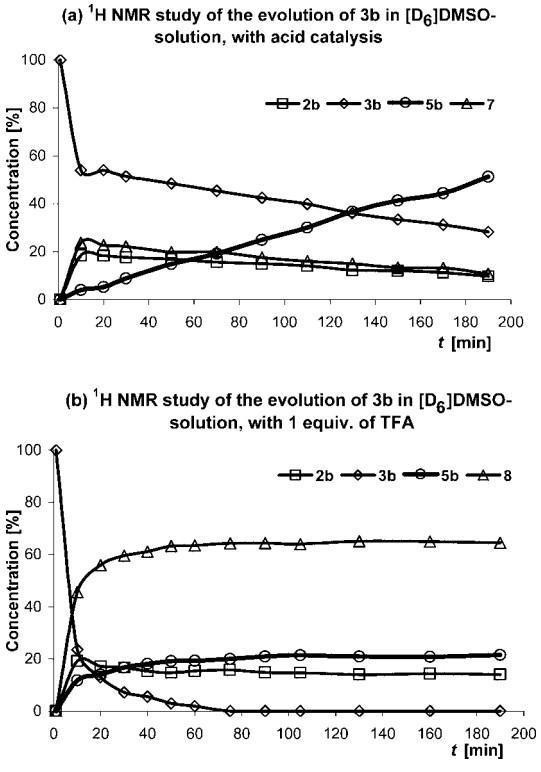


Figure 4. a) ^{1}H NMR study of the reaction behaviour of bi-imidazole **3b** (✧) in [D$_6$]DMSO solution (2 mg in 600 μL) at 20 °C, in the presence of TFA catalysis. Other compounds detected in solution: imidazole **2b** (□), **7** (Δ) and purine **5b** (○). b) ^{1}H NMR study of the reaction behaviour of bi-imidazole **3b** (✧) in [D$_6$]DMSO solution (2 mg in 600 μL) at 20 °C, in the presence of 1 equivalent of TFA. Other compounds detected in solution: imidazole **2b** (□), purine **5b** (○) and **8** (Δ).

between the acidic N–H and the imidazole nitrogen (**3A**) and the other between the same N–H and the oxygen of the double bond (**3B**) (Scheme 3).

From **3A** no further reaction occurs, and ring-opening may reverse the equilibrium back to imidazole **2**, as the zwitterion **2A**, in equilibrium with the neutral compound **2B**. From **3B**, ring-opening may proceed to give the intermediate isocyanates **4**, the common precursors of bi-imidazoles **7** (pathway *b*) and purines **5** (pathway *a*). Bi-imidazoles **7** are the result of intramolecular cyclization involving the amino and the isocyanate groups. Purines **5** are formed when intramolecular cyclization involves the imino and isocyanate groups. Dynamic equilibria between compounds **4** and **7** may ultimately result in the formation of purines **5** as the only products.

Ring-opening of **3b** to generate the intermediate **4** is accelerated by acid catalysis (trifluoroacetic acid). The addition of one equivalent of acid to a solution of compound **3b** (2 mg) in [D$_6$]DMSO (600 μL) resulted in a mixture of imidazoles **2b** and **3b**, which completely reacted to give bi-imidazole **8** through hydrolysis of the exocyclic imine bond.

Conclusions

The reactions between 5-amino-4-(cyanoformimidoyl)-imidazole and isocyanates after addition of DBU can be considered an efficient synthetic method for 4,4′-biimidazolyl-2-ones except when tosyl or acyl isocyanates are used. In those cases the biimidazole-2-ones spontaneously react further, in solution, to give 6-carboxamidinopurines, which are also isolated in excellent yields. The mechanism for this reaction does not depend on the substituent on the

imidazole nitrogen, as alkyl and aryl imidazoles follow a similar pathway (Scheme 1). The reaction is slow when compounds **2b** or **3b** are used as starting materials and their reaction behaviour, followed by ^{1}H NMR in a [D$_6$]DMSO solution, shows the formation of a fourth compound (together with structures **2**, **3** and **5**) tentatively identified as **7**. This compound was not detected when the study was performed with compounds **2a**, **3a**, **2e** and **3e**. These reactions are much faster and the only products detectable by ^{1}H NMR are compounds **2**, **3** and **5**. Addition of a catalytic amount of trifluoroacetic acid catalyses the formation of the purine ring from the bi-imidazoles **3**, but the use of one equivalent of acid results in the formation of a different product identified as **8**. The *N*-tosyl and *N*-acyl amidine functions in the 6-positions of purines **5** proved to be excellent precursors of the amidrazone substituent by nucleophilic substitution with hydrazine.

Experimental Section

General Remarks: The (*Z*)-*N*^{1}-(2-amino-1,2-dicyanovinyl)-*N*^{2}-aryl- and -*N*^{2}-methylformamidines and the 5-amino-1-aryl-4-(cyanoformimidoyl)imidazoles used in this work were prepared by previously described procedures.[13] NMR spectra were recorded on a Varian Unity Plus instrument (^{1}H: 300 MHz, ^{13}C: 75 MHz), including the ^{1}H–^{13}C correlation spectra (HMQC and HMBC), and deuterated DMSO was used as solvent. IR spectra were recorded on a Bomem MB 104 FT-IR instrument with use of Nujol mulls and NaCl cells. The reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254} (Merck). The melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed on a LECO CHNS-932 instrument.

General Procedure for the Preparation of 4-[(*N*-Acylcarbamoyl)-cyanoformimidoyl]-5-amino-1*H*-imidazoles (2): A suspension of **1** in dry acetonitrile (8–12 mL) was stirred under N_2 at 0 to –15 °C for 5–10 min. After 10 min the isocyanate (1.4–2.5 molar equivalents) was added to the mixture, which was stirred at low temperature until no starting material was detectable by TLC. The yellow/orange suspension was filtered and washed with acetonitrile and diethyl ether to give compounds **2a**–**d**.

5-Amino-4-[(*N*-ethoxycarbonylcarbamoyl)cyanoformimidoyl]-1-(4-methoxyphenyl)-1*H*-imidazole (2a): Yield 2.97 mmol, 100%; m.p. 175–178 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.50 (s, 1 H), 8.45 (s, 2 H), 7.61 (s, 1 H), 7.45 (d, J = 9.0 Hz, 2 H), 7.14 (d, J = 9.0 Hz, 2 H), 4.10 (q, J = 7.0 Hz, 2 H), 3.83 (s, 3 H), 1.21 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 159.9, 157.3, 151.9, 151.4, 138.6, 136.6, 127.5, 125.4, 122.5, 115.5, 112.5, 60.7, 55.6, 14.3 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3390, 3313, 3200, 2232 (CN), 1759, 1675, 1631 cm^{-1}. $C_{16}H_{16}N_6O_4$ (356.34) calcd. C 53.93, H 4.53, N 23.58; found C 54.02, H 4.78, N 23.89.

5-Amino-4-[(*N*-ethoxycarbonylcarbamoyl)cyanoformimidoyl]-1-(2-hydroxyethyl)-1*H*-imidazole (2b): Yield 2.05 mmol, 73%; m.p. 142–144 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.35 (s, 1 H), 8.65 (s, 2 H), 7.49 (s, 1 H), 5.07 (s, 1 H), 4.11 (q, J = 7.0 Hz, 2 H), 3.96 (t, J = 5.0 Hz, 2 H), 3.64 (t, J = 5.0 Hz, 2 H), 1.23 (t, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 157.4, 152.01, 151.98, 139.7, 135.8, 123.5, 112.0, 60.6, 58.6, 45.6, 14.3 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3376, 3293, 3152, 2230 (CN), 1755, 1650 cm^{-1}. $C_{11}H_{14}N_6O_4.H_2O$ (312.29) calcd. C 42.31, H 5.16, N 26.917; found C 42.45, H 5.33, N 26.87.

5-Amino-4-[(*N*-benzoylcarbamoyl)cyanoformimidoyl]-1-(4-methoxyphenyl)-1*H*-imidazole (2c): Yield 1.51 mmol, 91%; m.p. 207 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.90 (s, 1 H), 8.69 (s, 2 H), 7.84 (d, J = 7.5 Hz, 2 H), 7.67 (s, 1 H), 7.60 (t, J = 7.5 Hz, 1 H), 7.52 (t, J = 7.5 Hz, 2 H), 7.47 (d, J = 9.0 Hz, 2 H), 7.14 (d, J = 9.0 Hz, 2 H), 3.83 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 166.7, 159.8, 157.8, 151.7, 139.2, 136.4, 134.4, 132.2, 128.4, 128.2, 127.4, 125.4, 123.2, 115.2, 112.5, 55.6 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3557, 3450, 3085, 2222 (CN), 1748, 1712, 1691, 1674, 1643 cm^{-1}. $C_{20}H_{16}N_6O_3$ (388.39) calcd. C 61.85, H 4.15, N 21.64; found C 61.72, H 4.19, N 21.45.

5-Amino-4-[(*N*-benzoylcarbamoyl)cyanoformimidoyl]-1-[2-(benzoylcarbamoyloxy)ethyl]-1*H*-imidazole (2d): Yield 3.13 mmol, 95%; m.p. 150 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 11.02 (s, 1 H), 10.80 (s, 1 H), 9.00 (s, 2 H), 7.85 (d, J = 7.5 Hz, 2 H), 7.83 (d, J = 7.5 Hz, 2 H), 7.66 (s, 1 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.60 (m, 1 H), 7.51 (t, J = 7.5 Hz, 2 H), 7.49 (d, J = 7.5 Hz, 2 H), 4.40 (t, J = 5.0 Hz, 2 H), 4.25 (t, J = 5.0 Hz, 2 H) ppm. ^{13}C NMR ([D$_6$]-DMSO, 75 MHz): δ = 170.4, 167.6, 158.0, 151.0, 141 (br.) 136.7 (br.), 133.9, 133.7, 132.8, 129.6, 129.5, 129.3, 129.0, 128.2, 124.6, 63.8, 43.0 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3310, 3350, 3170, 2219 (CN), 1770, 1720, 1660, 1640 cm^{-1}. $C_{23}H_{19}N_7O_5{\cdot}H_2O$ (491.46) calcd. C 56.21, H 4.31, N 19.95; found C 56.50, H 4.24, N 19.50.

Reaction between 5-Amino-4-(cyanoformimidoyl)-1-methylimidazole (1c) and Benzoyl Isocyanate. Formation of 2e and 5e: A suspension of imidazole **1c** (0.40 g, 2.69 mmol) in dry acetonitrile (25 mL) was stirred under nitrogen at –15 °C for 5 min. Addition of benzoyl isocyanate (0.59 g, 4.03 mmol) produced an orange suspension. After stirring for 30 min at –15 °C, the orange solid was filtered under nitrogen and washed with acetonitrile and diethyl ether. The solid was identified as **2e**; 0.55 g, 1.85 mmol, 70%); m.p. 225 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.80 (s, 1 H), 8.86 (s, 2 H), 7.85 (d, J = 7.5 Hz, 2 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.55 (s, 1 H), 7.51 (t, J = 7.5 Hz, 2 H), 3.47 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 166.6, 157.9, 152.6, 140.2, 134.4, 132.2, 128.4, 128.2, 124.4, 112.7, 30.2 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3609, 3583, 3300, 3160, 1712, 1657, 1638 cm^{-1}. $C_{14}H_{12}N_6O_2{\cdot}1/4\,H_2O$ (300.79) calcd. C 55.90, H 4.19, N 27.94; found C 56.13, H 4.31, N 27.97.

The mother liquor was stirred at –15 °C for a further 2 h, resulting in a yellow solid, which was filtered and washed with acetonitrile and diethyl ether. The solid was identified as **5e** (0.03 g, 0.10 mmol, 4%); m.p. 265 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 11.80 (br. s, 1 H), 10.10 (br. s, 1 H), 9.15 (br. s, 1 H), 8.44 (s, 1 H), 8.32 (d, J = 7.5 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 2 H), 3.65 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 178.4, 160.0, 158.8, 157.9, 149.2, 144 (br.), 136.7, 132.3, 129.6, 128.1, 124.3, 29.3 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3350, 3240, 3127, 3060, 1720, 1637 cm^{-1}. Elemental analysis (%) for $C_{14}H_{12}N_6O_2$ (296.29) calcd. C 56.75, H 4.08, N 28.36; found C 56.91, H 4.22, N 28.12.

Reaction between 5-Amino-4-(cyanoformimidoyl)-1-methylimidazole (1c) and Tosyl Isocyanate Formation of 2f and 5f. Method A: A solution of imidazole **1c** (0.40 g, 2.69 mmol) in dry acetonitrile (35 mL) was stirred under nitrogen in an ice/salt bath (–4 °C). After 3 min, tosyl isocyanate (1.07 g, 5.45 mmol) was added, producing an orange suspension. After 10 min at –4 °C, the solid was filtered off and washed with acetonitrile and diethyl ether. The product was identified as **2f** (0.11 g, 0.32 mmol, 12%); m.p. 260 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 11.60 (br. s, 1 H), 8.52 (br. s, 2 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.51 (s, 1 H), 7.42 (d, J = 8.0 Hz, 2 H),

3.44 (s, 3 H), 2.38 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 157.9, 152.6, 140.6, 129.5, 127.4, 30.2, 21.1 ppm (the remaining signals are not visible in the spectrum due to the rapid further transformation into **3f** and **5f**). $C_{14}H_{14}N_6O_3S\cdot1.25\,H_2O$ (368.88) calcd. C 45.58, H 4.51, N 22.78, S 8.93; found C 45.58, H 4.47, N 23.08, S 8.74. The following signals in the NMR spectra were assigned to compound **3f**: ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.60 (s, 1 H), 8.12 (s, 2 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.67 (s, 1 H), 7.42 (d, J = 8.0 Hz, 2 H), 3.44 (s, 3 H), 2.38 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 159.7, 156.2, 154.1, 152.7, 145.2, 141.7, 135.7, 129.8, 127.5, 114.7, 30.3, 20.9 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3584, 3556, 2255, 1668, 1648, 1587 cm^{-1}. The mother liquor was stirred at room temperature for 45 min. The yellow suspension was filtered off and washed with acetonitrile and diethyl ether. The product was identified as **5f** (0.74 g, 2.14 mmol, 79%); m.p. 290 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 12.10 (br. s, 1 H), 9.17 (br. s, 1 H), 8.67 (br. s, 1 H), 8.42 (s, 1 H), 7.84 (d, J = 8.0 Hz, 2 H), 7.36 (d, J = 8.0 Hz, 2 H), 3.69 (s, 3 H), 2.37 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 160.2, 157.8, 156.7, 147.8, 146 (br.), 145.2, 135.7, 129.8, 128.0, 127.5, 29.5, 20.9 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3410, 3300, 1638, 1600 cm^{-1}. $C_{14}H_{14}N_6O_3S$ (346.37) calcd. C 48.55, H 4.07, N 24.26, S 9.26; found C 48.28, H 4.15, N 23.95, S 9.00.

Method B: A solution of imidazole **1c** (0.10 g, 0.67 mmol) in dry acetonitrile (30 mL) was stirred under nitrogen in an ethylene glycol/dry ice bath (–15 °C). After 30 min, tosyl isocyanate (0.26 g, 1.34 mmol) was added, producing an orange suspension. After 10 min at low temperature, the solid was filtered off under nitrogen and washed with cold acetonitrile. The product was identified as **2f** (0.09 g, 0.26 mmol, 39%). A yellow solid precipitated from the mother liquor and was filtered and washed with acetonitrile and diethyl ether. The product was identified as **5f** (0.12 g, 0.35 mmol, 52%).

General Procedure for the Synthesis of 4,4′-Bi-1*H*-imidazoles 3: A suspension of the imidazole **2** in acetonitrile (3–6 mL) was stirred at room temperature. Addition of DBU (0.05–0.2 molar equivalents) resulted in an immediate change in the colour of the suspension, which turned from yellow to orange. The mixture was stirred at room temperature for 5 min to 2.5 h. The orange solid was filtered off and washed with acetonitrile and diethyl ether to give compounds **3a**–**c**.

Ethyl 5′-Amino-5-imino-1′-(4-methoxyphenyl)-2-oxo-2,5-dihydro-4,4′-bi-1*H*-imidazole-1-carboxylate (3a): Yield 0.76 mmol, 88%; m.p. 170 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.80 (s, 1 H), 8.00 (s, 2 H), 7.89 (s, 1 H), 7.49 (d, J = 9.0 Hz, 2 H), 7.18 (d, J = 9.0 Hz, 2 H), 4.37 (q, J = 7.0 Hz, 2 H), 3.82 (s, 3 H), 1.30 (t, J = 7.0 Hz, 3 H) ppm. The sample was not soluble enough in [D$_6$]-DMSO for ^{13}C NMR spectroscopy. IR (Nujol mull): $\tilde{\nu}$ = 3255, 3200, 3090, 1750, 1712, 1646, 1623, 1614 cm^{-1}. $C_{16}H_{16}N_6O_4$ (356.34) calcd. C 53.93, H 4.53, N 23.58; found C 54.05, H 4.75, N 23.67.

Ethyl 5′-Amino-1′-(2-hydroxyethyl)-5-imino-2-oxo-2,5-dihydro-4,4′-bi-1*H*-imidazol-1-carboxylate (3b): Yield 0.28 mmol, 82%; m.p. 199 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.75 (s, 1 H), 8.10 (s, 2 H), 7.65 (s, 1 H), 4.30 (q, J = 7.0 Hz, 2 H), 3.96 (t, J = 5.0 Hz, 2 H), 3.63 (t, J = 5.0 Hz, 2 H), 1.28 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 156 (br.), 154 (br.), 152 (br.), 150.0, 61.9, 58.4, 45.0, 14.0 ppm (the remaining signals are not visible in the spectrum). IR (Nujol mull): $\tilde{\nu}$ = 3300, 3280, 3180, 1741, 1646, 1602 cm^{-1}. $C_{11}H_{14}N_6O_4\cdot1/4\,H_2O$ (298.77) calcd. C 44.22, H 4.89, N 28.13; found C 44.05, H 4.85, N 28.11.

5′-Amino-1-benzoyl-5-imino-1′-(4-methoxyphenyl)-4,4′-bi-1*H*-imidazol-2(5*H*)-one (3c): Yield 0.32 mmol, 82%; m.p. 252 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.40 (s, 1 H), 7.96 (s, 2 H), 7.86 (s, 1 H), 7.86 (d, J = 7.2 Hz, 2 H), 7.67 (m, 1 H), 7.50 (t, J = 8.0 Hz, 2 H), 7.49 (d, J = 9.0 Hz, 2 H), 7.16 (d, J = 9.0 Hz, 2 H), 3.83 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 168.0, 160.2, 159.9, 159.9, 140.1, 133.7, 130.0, 128.8, 128.4, 127.4, 125.4, 115.2, 55.6 ppm (note: three peaks are not visible). IR (Nujol mull): $\tilde{\nu}$ = 3363, 3263, 3250, 1737, 1686, 1642, 1603 cm^{-1}. MS (FAB) *m*/*z* (rel. int.) 367 [M + 1]$^+$, 93. HRMS (FAB) *m*/*z* for $C_{20}H_{16}N_6O_3$ calcd. 389.1362; found 389.1352.

Cyclization of 2d with DBU. Method A: A solution of DBU (0.02 g, 0.14 mmol) in acetonitrile (25 mL) was added to imidazole **2d** (0.27 g, 0.57 mmol). The orange suspension was stirred at room temperature for 15 min, producing an orange solid, which was filtered off and washed with acetonitrile and diethyl ether. The solid was identified as the starting material **2d** (0.12 g, 0.25 mmol, 43%). The mother liquor was concentrated in the rotary evaporator to provide a yellow solid that was filtered and washed with acetonitrile and diethyl ether. The product was identified as the 6-amidinopurine **5d** (0.07 g, 0.15 mmol 26%); m.p. 219 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 11.4–11.2 (br. s, 1 H), 11.00 (s, 1 H), 10.2 (br. s, 1 H), 9.15 (br. s, 1 H), 8.59 (s, 1 H), 8.32 (d, J = 8.0 Hz, 2 H), 7.82 (d, J = 7.5 Hz, 2 H), 7.6–7.5 (m, 2 H), 7.5–7.4 (m, 4 H), 4.51 (t, J = 5.0 Hz, 2 H), 4.44 (t, J = 5.0 Hz, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 178.5, 166.0, 158.8, 158.5, 158.0, 151.2, 148.9, 143.6, 136.7, 133.3, 132.6, 132.3, 129.6, 128.4, 128.3, 128.2, 124.3, 62.8, 42.0 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3366, 3316, 3100, 1794, 1698, 1695, 1600 cm^{-1}. $C_{23}H_{19}N_7O_5\cdot1/4\,H_2O$ (477.95) calcd. C 57.80, H 4.11, N 20.51; found C 57.90, H 4.33, N 20.75.

Method B: A solution of DBU (0.02 g, 0.14 mmol) in acetonitrile (25 mL) was added to imidazole **2d** (0.10 g, 0.22 mmol). After 4 h at 0 °C, the solid was filtered off and washed with acetonitrile and diethyl ether. The solid was identified as the starting material **2d** (0.03 g, 0.06 mmol, 26%). The mother liquor was stirred at 4 °C for 6 d, but no product could be isolated because of extensive decomposition.

Cyclization of 2e in the Presence of Base. Method A: Imidazole **2e** (0.20 g, 0.68 mmol) was added to a solution of DBU (0.002 g, 0.01 mmol) in acetonitrile (15 mL) and the mixture was stirred at 0 °C. A different yellow suspension immediately developed and the mixture was stirred for 15 min. The solid was filtered off and washed with acetonitrile and diethyl ether. The product was identified as **3e**; 0.18 g, 0.60 mmol, 88%); m.p. 236 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.44 (s, 1 H), 8.06 (br. s, 2 H), 7.84 (d, J = 7.5 Hz, 2 H), 7.67 (s, 1 H), 7.66 (t, J = 7.5 Hz, 1 H), 7.50 (t, J = 7.5 Hz, 2 H), 3.50 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 167.9, 163.2, 158.6, 155.5, 153.6, 140.8, 133.6, 130.0, 129.6, 128.4, 114.2, 30.2 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3380, 3240, 1744, 1675, 1666, 1656, 1609 cm^{-1}. $C_{14}H_{12}N_6O_2\cdot1/4\,H_2O$ (300.79) calcd. C 55.90, H 4.19, N 27.94; found C 55.95, H 4.35, N 27.69.

Method B: Triethylamine (0.04 g, 0.41 mmol) was added to a suspension of imidazole **2e** (0.12 g, 0.41 mmol) in acetonitrile (4 mL). The mixture was stirred at room temperature for 15 min and the yellow solid was filtered off and washed with acetonitrile and diethyl ether. The product was identified as **3e** (0.11 g, 0.37 mmol, 90%). The mother liquor was stirred at room temperature and after one day the solvent was partially removed in the rotary evaporator and the solid was filtered off and washed with acetonitrile and diethyl ether. The product was identified as purine **5e** (0.005 g, 0.02 mmol, 4%).

General Procedure for the Synthesis of 2-Oxo-2,9-dihydro-1*H*-purine-6-carboxamidines 5 from 2. Method A: A suspension/solution of an imidazole **2** in DMF (5–30 mL) was stirred at 0 °C to 23 °C for 7 h–1 d. The final suspension (resulting from spontaneous precipitation of the product or from addition of water to the DMF solution) was filtered off and washed with ethanol and diethyl ether to give the corresponding compound **5a**–**d**.

Method B: A suspension/solution of an imidazole **2** in ethanol (15–50 mL) was stirred at 10 °C to 23 °C for 3–12 d. The suspension was filtered and washed with EtOH and Et_2O to give the corresponding compound **5a**–**e**.

Ethyl 6-Amidino-9-(4′-methoxyphenyl)-2-oxo-2,9-dihydro-1*H*-purine-*N*²-carboxylate (5a): Yield 1.06 mmol, 84%; m.p. 202–203 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 11.00–9.00 (br. s, 1 H), 8.90 (br. s, 1 H), 8.73 (s, 1 H), 7.69 (d, J = 9.0 Hz, 2 H), 7.14 (d, J = 9.0 Hz, 2 H), 4.06 (q, J = 7.0 Hz, 2 H), 3.82 (s, 3 H), 1.19 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 163.0, 160.0, 159.4, 158.9, 157.0, 146.4, 126.9, 125.9, 125.3, 114.7, 60.7, 55.6, 14.3 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3376, 3287, 3130, 3105, 1666, 1610 cm^{-1}. MS (EI, 70 eV) *m*/*z* (rel. int.) 356 [M]$^+$ (4). $C_{16}H_{16}N_6O_4$ (356.34) calcd. C 53.93, H 4.53, N 23.58; found C 53.87, H 4.51, N 23.45.

Ethyl 6-Amidino-9-(2′-hydroxyethyl)-2-oxo-2,9-dihydro-1*H*-purine-*N*²-carboxylate (5b): Yield 0.54 mmol, 76%; m.p. 216 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 11.00–9.00 (br. s, 1 H), 8.90 (br. s, 1 H), 8.40 (s, 1 H), 5.01 (br. s, 1 H), 4.14 (t, J = 5.0 Hz, 2 H), 4.07 (q, J = 7.0 Hz, 2 H), 3.73 (t, J = 5.0 Hz, 2 H), 1.19 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 162.8 (br.), 159.5 (br.), 158.3, 158.0, 148.7, 144.1 (br.), 124.7, 60.7, 58.7, 45.7, 14.2 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3370, 3360, 3300, 3097, 1744, 1670, 1637 cm^{-1}. $C_{11}H_{14}N_6O_4$ (294.27) calcd. C 44.90, H 4.80, N 28.56; found C 44.93, H 4.79, N 28.30.

***N*²-Benzoyl-9-(4′-methoxyphenyl)-2-oxo-2,9-dihydro-1*H*-purine-6-carboxamidine (5c):** Yield 0.32 mmol, 84%; m.p. 237 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 11.2 (s, 1 H), 10.0 (br. s, 1 H), 9.20 (br. s, 1 H), 8.77 (s, 1 H), 8.32 (d, J = 7.0 Hz, 2 H), 7.72 (d, J = 9.0 Hz, 2 H), 7.58 (m, 1 H), 7.49 (t, J = 7.5 Hz, 2 H), 7.16 (d, J = 9.0 Hz, 2 H), 3.83 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): DBU salt, δ = 165.5, 156.2, 162.8, 157.8, 157.1, 148.8, 140.1, 133.6, 132.5, 129.0, 128.7, 128.3, 124.2, 121.8, 114.3, 55.4, 53.2, 47.8, 37.7, 31.4, 28.3, 26.0, 23.5, 19.0 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3360, 3200, 3170, 3120, 1640, 1620 cm^{-1}. $C_{20}H_{16}N_6O_3$ (388.39) calcd. C 61.85, H 4.15, N 21.64; found C 61.59, H 4.31, N 21.50.

Method C: Trifluoroacetic acid (0.05 mmol; 0.006 g) was added to a suspension of imidazole **2e** (0.12 g, 0.41 mmol) in acetonitrile (4 mL) and the mixture was stirred at room temperature for 20 min. The suspension was filtered and washed with ethanol and diethyl ether, and the product was identified as **5e** (0.11 g, 0.38 mmol, 92%).

Synthesis of Purine 5a from 3a. Method A: A suspension of **3a** (0.10 g, 0.29 mmol) in ethanol (15 mL) was stirred at room temperature for 11 d. The yellow solid was filtered off and washed with ethanol and diethyl ether. The product was identified as **5a** (0.17 g, 0.06 mmol, 57%).

Method B: A suspension of **3a** (0.08 g, 0.23 mmol) in DMF (1 mL) was stirred at 4 °C for 23 h. The yellow solid was filtered off and washed with EtOH and Et_2O. The product was identified as **5a** (0.06 g, 0.17 mmol, 73%).

Synthesis of Purine 5e from 3e: A suspension of **3e** (0.13 g, 0.44 mmol) in ethanol (15 mL) was stirred at room temperature for 12 d. The yellow solid was filtered off and washed with ethanol and diethyl ether. The product was identified as **5a** (0.11 g, 0.37 mmol, 86%).

Preparation of 9-(4′-Methoxyphenyl)-2-oxo-2,9-dihydro-1*H*-purine-6-carboxamidrazone (6). From 5a: Hydrazine hydrate (2.65 g, 2.60 mmol) was added to a suspension of **5a** (0.30 g, 0.83 mmol) in ethanol (20 mL) and the mixture was stirred at room temperature for 18 h. The yellow suspension was filtered off and washed with ethanol and diethyl ether, and the product was identified as **6** (0.25 g, 0.83 mmol, 99.6%); m.p. 350 °C (dec.). ^{1}H NMR ([D$_6$]-DMSO, 300 MHz): δ = 10.0–8.0 (br. s, 1 H), 8.57 (s, 1 H), 7.67 (d, J = 9.0 Hz, 2 H), 7.11 (d, J = 9.0 Hz, 2 H), 3.81 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 160.3, 158.6, 156.0, 146.1, 140 (br.), 127.0, 125.1, 120.0, 114.5, 55.4 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3360, 3312, 3211, 1643, 1620 cm^{-1}. MS (EI, 70 eV) *m*/*z* (rel. int.) 299 [M]$^+$ (13). $C_{13}H_{13}N_7O_2 \cdot 1/4\,H_2O$ (303.80) calcd. C 51.40, H 4.48, N 32.27; found C 51.67, H 4.49, N 32.37.

From 5c: Hydrazine hydrate (0.06 g, 1.16 mmol) was added to a suspension of **5c** (0.23 g, 0.58 mmol) in ethanol (20 mL) at room temperature. After stirring for 2 d at room temperature, the yellow solid was filtered off and washed with ethanol and diethyl ether. The product was identified as **6** (0.17 g, 0.57 mmol, 98%).

From 5g: Hydrazine hydrate (0.10 g, 2.02 mmol) was added to a suspension of **5g** (0.34 g, 0.78 mmol) in acetonitrile (20 mL) at room temperature. After the mixture had been stirred at room temperature for 3 d, ethanol was added to precipitate the solid, which was filtered off and washed with ethanol and diethyl ether. The product was identified as **6** (0.18 g, 0.61 mmol, 79%).

Synthesis of Ethyl 5′-Amino-1′-(2-hydroxyethyl)-2,5-dioxo-2,5-dihydro-4,4′-bi-1*H*-imidazole-1-carboxylate (8): Trifluoroacetic acid (0.06 g, 0.52 mmol) was added to a suspension of **3b** (1.41 g, 0.50 mmol) in DMSO (1 mL) and the mixture was stirred at room temperature. The yellow suspension turned orange immediately after the addition of the acid. No apparent change had occurred after 5 h at room temperature and the mixture was allowed to stand at –18 °C for 2 d. The orange solid was filtered off and washed with ethanol and diethyl ether. The product was identified as the title compound (0.10 g, 0.33 mmol, 66%); m.p. 186 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.56 (br. s, 2 H), 7.59 (s, 1 H), 5.08 (br. s, 1 H), 4.29 (q, J = 7.2 Hz, 2 H), 3.96 (t, J = 4.8 Hz, 2 H), 3.63 (t, J = 4.5 Hz, 2 H), 1.28 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 161.0, 159.5, 155.9, 151.85, 148.3, 142.5, 115.5, 62.9, 58.6, 45.8, 14.0 ppm. IR (Nujol mull): $\tilde{\nu}$ = 3582, 3472, 3341, 1781, 1745, 1698, 1650, 1610 cm^{-1}. $C_{11}H_{13}N_5O_5 \cdot H_2O$ (313.27) calcd. C 42.17, H 4.83, N 22.36; found C 42.34, H 4.99, N 21.93.

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