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The Reactions of Diaminomaleonitrile with Isocyanates and Either Aldehydes or Ketones Revisited

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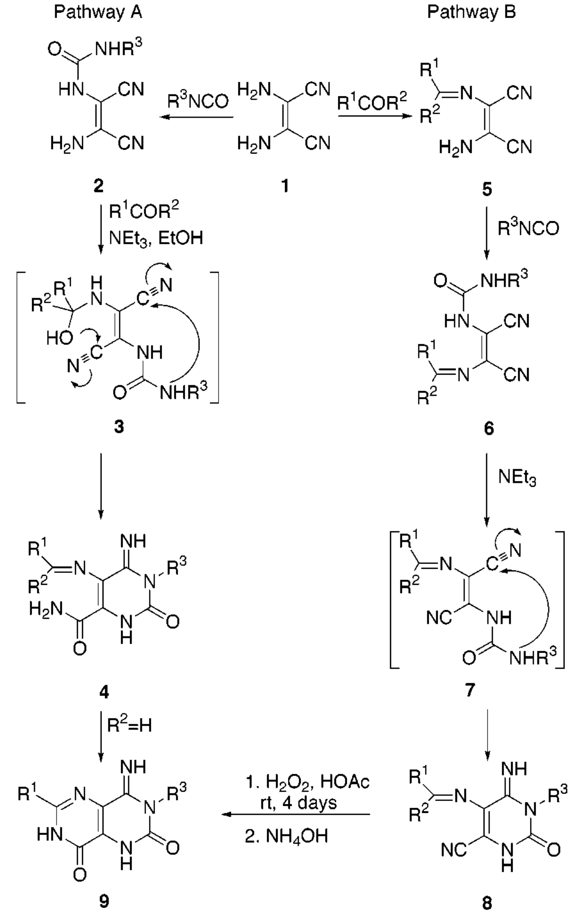
A reinvestigation of the reactions of urea derivatives of diaminomaleonitrile **2** with aldehydes or ketones in the presence of triethylamine has established that the products of these reactions are not pyrimidino[5,4-*d*]pyrimidines **9** as previously reported, but 8-oxo-6-carboxamido-1,2-dihydropurines **12**, which are oxidized rapidly in air to the corresponding 6-carboxamidopurines **13**. Similarly, the reaction of Schiff base derivatives of DAMN **5** with isocyanates in the presence of triethylamine gives the substituted 2-oxoimidazoles **20** and not the pyrimidine derivatives **8** as previously claimed. The compounds **20** cyclize in solution and are easily oxidized to 8-oxopurine-6-carbonitriles **22,** which give the same 8-oxopurine-6-carboxamides **13** upon further hydrolysis.

Introduction

Diaminomaleonitrile (DAMN, **1**), a tetramer of hydrogen cyanide, is a versatile precursor to a number of nitrogen heterocycles, which include imidazoles and purines,[1] pyrroles,[2] pyrimidines, [3] pyrazines, [4] diazepines, [1b,5] and triazepines.[6]

A previous detailed study[7] of the reaction of DAMN with isocyanates together with either an aldehyde or a ketone in the presence of triethylamine reported that the products of these reactions were pyrimidino[5,4-*d*]pyrimidines **9**, formed either by pathways A or B as shown in Scheme 1. The author was able to isolate an intermediate supposed to have structure **6** and to show that it was thermally stable in hot acetonitrile. In the presence of base, the author postulated that isomerization occurs around the C=C bond to give an intermediate **7**, which cyclizes rapidly to **8**; compound **7** could never be isolated. In pathway A, double-bond isomerization is again proposed under base-catalysis during the condensation of **2** with the aldehyde or ketone. Intermediate **3** could not be isolated and this was attributed to its rapid cyclization to pyrimidine **4**, and subsequent cyclization followed by oxidation in air to give the isolated product, assigned

Scheme 1



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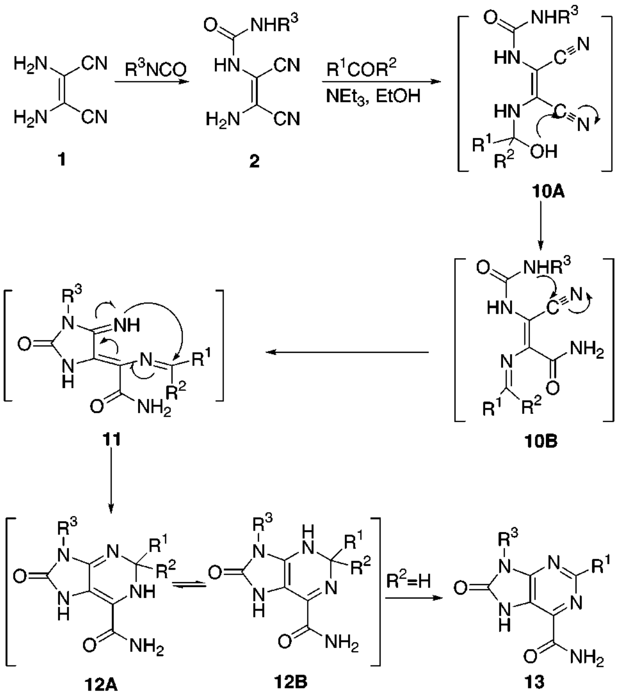
Scheme 2



Compound	R^1	R^2	R^3	Reaction Conditions	Yield (%)
2a	-	-	Ph	24 h (rt)	95
2b	-	-	CH_2Ph	1 h (0°C) 18 h (rt)	82
12a	CH_3	CH_3	Ph	24 h (rt)	64
12b	4-$MeOC_6H_4$	H	Ph	19 h (rt)	82
12c	-$CH_2CH_2SCH_2CH_2$-		Ph	19 h (rt)	50
12d	-$CH_2(CH_2)_3CH_2$-		Ph	19 h (rt)	64
13a	Ph	-	Ph	1 h (rt)$^{a)}$	68$^{a)}$
13b	4-$MeOC_6H_4$	-	Ph	1 h (reflux)$^{b)}$	50$^{b)}$
13c	4-CNC_6H_4	-	Ph	18 h (rt)$^{a)}$	69 $^{a)}$
13d	4-$NO_2C_6H_4$	-	Ph	18 h (rt)$^{a)}$	90$^{a)}$
13e	CH_3	-	Ph	19 h (rt)$^{a)}$	78$^{a)}$
13f	4-$MeOC_6H_4$	-	CH_2Ph	72 h (rt)$^{a)}$	70$^{a)}$

$^{a)}$From **2** and aldehyde, in NEt_3.

$^{b)}$From **12b**, in ethanol.

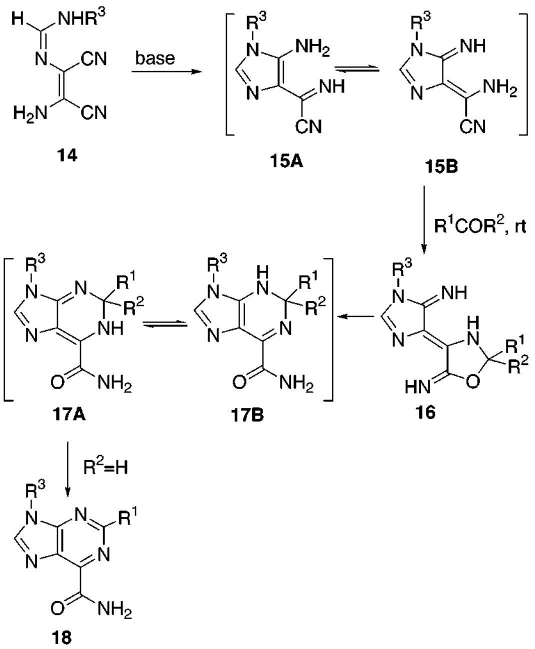
structure **9**. The same product was also obtained from **8** after prolonged hydrolysis of the cyano group using hydrogen peroxide in acetic acid.

For some time, we have been interested in the geometrical isomerism of DAMN derivatives in the belief that this type of reaction is much more common than is supposed in the current literature. For this reason, we were intrigued by the above report by Ohtsuka and decided to reinvestigate his reactions to try to confirm that isomerism does occur under the conditions he had outlined.

Results and Discussion

The reactions of DAMN with phenyl or benzyl isocyanate proceeded as expected to give the urea derivatives **2a** and **2b** in excellent yields (Scheme 2). Compound **2a** has been previously described by Ohtsuka[7] and our spectroscopic data are in complete agreement with his. Compound **2b** has not been reported previously, but has the characteristic nitrile absorptions at 2249 and 2205 cm^{-1} and the carbonyl absorption at 1644 cm^{-1} in the IR spectrum. On reaction of **2** with aldehydes or ketones (either as neat liquids or in methanol) in the presence of triethylamine at room temperature, white-pale yellow solids precipitated in good yields exactly as described by Ohtsuka and previously assigned the pyrimidine structure **4**. Although our spectroscopic data for **4** ($R^1 = R^2 =$ Me, $R^3 =$ Ph) are in good agreement with those reported,[7] we now believe that this compounds is the 1,2-dihydropurine-6-carboxamide **12a** (see Scheme 2). Structures **4** and **12a** are isomeric and cannot be distinguished by elemental analysis. The main evidence for structure **12a** rather than **4** comes from a reassessment of the $^1H/^{13}C$ NMR spectroscopic data. In the ^1H NMR spectrum the two methyl groups are equivalent and appear at δ 1.31 and are clearly bonded to an sp^3 carbon atom, as substantiated by the peak at δ 70.11 ppm assigned to C-2 in the ^{13}C NMR spectrum. This is incompatible with the structure **4** in which the two methyl groups of the imine are nonequivalent and would be expected to show different chemical shift values, being bonded to an sp^2 carbon. The singlet at δ 4.97 (1H) is typical of the pyrimidine N–H in 1,2-dihydropurines,[8,9] while the singlet at δ 9.75 (1H) can be assigned to the acidic NH of the imidazole ring. Also typical of a 6-carboxamido group in 1,2-dihydropurines are the different chemical shifts of the amide protons, with one appearing as a singlet at δ 7.61 and the other as a singlet masked by the aromatic multiplet at δ 7.40–7.50 ppm. All the features compare well with those of 6-carboxamido-1,2-dihydropurines, previously reported[8,9] and prepared using the reactions described in Scheme 3. The closest analogues to the

Scheme 3



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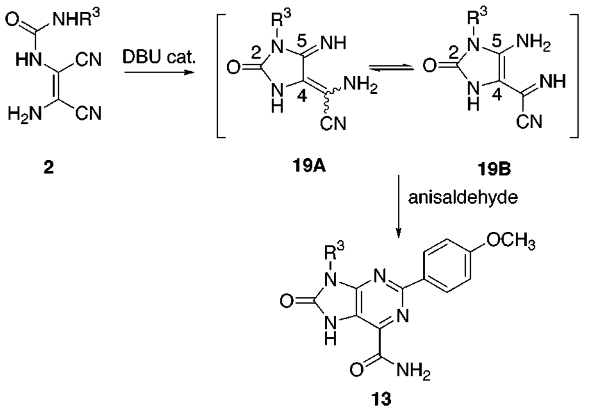
Scheme 4



2 19A 19B 13

Compound	R^3	Reaction Conditions	Yield (%)
19b	CH_2Ph	18 h (4°C)	74
13b	Ph	2 h (0°C)[a)] 6.5 h (rt)	47[a)]
13f	CH_2Ph	66 h (rt)[b)]	58[b)]

[a)] From **2a** and DBU, followed by addition of aldehyde

[b)] From **19b** and aldehyde

present work are the intermediates **16** ($R^1 = R^2 =$ Me, $R^3 =$ Ph)[8] and the tautomers **17A** and **17B** ($R^1 = R^2 =$ Me, $R^3 =$ Ph),[9] for which the structures have been fully established by X-ray crystallography. It is noteworthy that when $R^2 =$ H, compounds **17**, in solution, are rapidly oxidized to the corresponding purines **18**, which mirrors the reported behavior of compound **4**. Indeed, when **2a** or **b** were caused to react with aldehydes, the isolated product was the purine derivatives **13** rather than the dihydropurines **12** (see Scheme 2). The exception being the reaction between **2a** and *p*-anisaldehyde, where it was possible to isolate the intermediate **12b** (82%), when the solid product was removed from the reaction mixture after 10 min. at room temperature. The ^1H NMR spectrum of this compound shows coupling between the pyrimidine NH (δ 5.34, d, $J = 4.5$ Hz) and the adjacent CH proton (δ 5.67, d, $J = 4.5$ Hz), a clear indication of the 1,2-dihydropurine structure. On refluxing **12b** in ethanol over 1 h it oxidizes to **13b**, which was isolated in 50% yield.

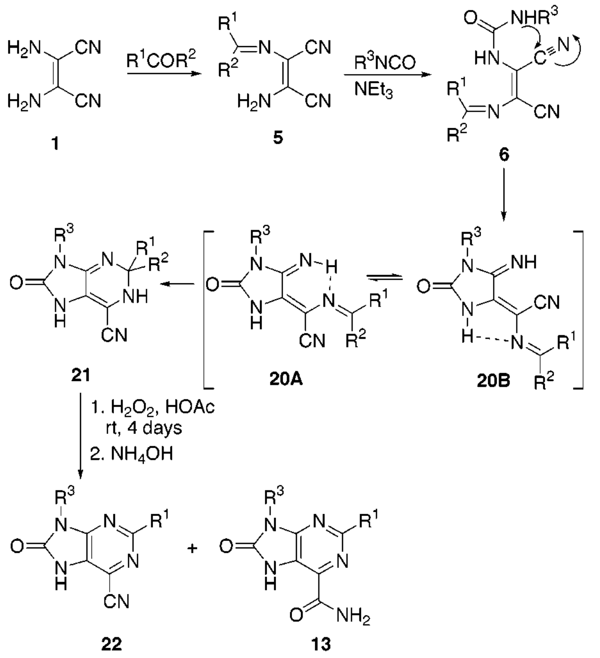
It can be seen from Scheme 3 that in the presence of a base the amidines **14** cyclize rapidly to a 5-amino-4-cyanoformimidoylimidazole intermediate **15**, which can be isolated when a mild base, such as DBU, is employed. It seemed reasonable to assume that a similar cyclization may occur with the urea derivatives **2** in the presence of base and this may provide an alternative synthetic route to compounds **12** and **13**. Consequently, a catalytic amount of DBU was added to a solution of **2b** in acetonitrile and a slow reaction occurred to give a new compound **19b** in 74% yield (Scheme 4). The IR spectrum of the yellow solid shows a single cyano absorption of medium intensity at 2214 cm^{-1} consistent with cyclization. In the ^1H and ^{13}C NMR spectra in DMSO-d_6, two sets of peaks can be seen consistent with the presence of the tautomers **A** and **B** in a 2:1 ratio. The identification of the tautomers was made on the basis of HMBC data, considering the three-bond interaction of the CH_2 and the NH/NH_2 protons. Careful analysis indicates that for the major isomer both the CH_2 (δ 4.68) and NH (δ 7.83) protons interact with C-5 (δ 153.6) and this establishes the structure as **19A**. Confirmation of this comes from the three-bonds interaction of the NH (δ 7.83) and the NH_2 (δ 5.61) protons with C-4 (δ 116.2). In contrast, in the minor isomer **19B** only the CH_2 protons (δ 4.72) interact with C-5 (δ 153.9), while the NH proton (δ 8.02) interacts with a signal at δ 150.5 ppm, assigned to the cyanoformimidoyl carbon atom, while the NH_2 protons (δ 5.32) interact with a ^{13}C signal at δ 114.5, which is thus attributed to C-4. When both the ^1H and ^{13}C NMR spectra were run at 70 °C, only one set of signals was observed, which coincide with those of tautomer **19A**, indicating that this is the more thermodynamically stable of the two tautomers. At this temperature, the ^1H NMR signals are slightly shifted from those observed at room temperature. So, for example, the imidazole NH moves from δ 10.70 (**19A**) and δ 10.40 (**19B**) at room temperature to δ 9.94 ppm, which may indicate that these protons are hydrogen bonded to a different extent with the DMSO solvent at room temperature.

The reaction of **19b** with 3 equiv of *p*-anisaldehyde in ethanol gave **13f** in 58% yield. This compound was identical to that isolated earlier in 70% yield from the reaction of **2b** with *p*-anisaldehyde and triethylamine in ethanol (see Scheme 2). All the carboxamido-8-oxopurines show two singlets, each one integrating for one proton, in the δ 8.50−8.60 and δ 7.90−8.00 ppm region for the NH protons of the 6-carboxamido group. An unusually sharp, one proton singlet in the region of δ 11.70−12.00 ppm can be assigned to the imidazole NH. In the ^{13}C NMR spectra the signals for C-2, C-4, and C-8 appear in the δ 152−155 region and the C=O around δ 165 ppm. Attempts to isolate the imidazole **19a** from **2a** and DBU under similar conditions failed as only a brown solution was obtained, but on addition of two equivalents of *p*-anisaldehyde to this solution the 6-carboxamidopurine **13a** was isolated in 47% yield, indicative of the formation of **19a**.

These results establish that the products of the urea derivatives **2** of DAMN with aldehydes or ketones in the presence of triethylamine are the 8-oxo-6-carboxamido-1,2-dihydropurines **12**, which in the case of aldehydes, are readily oxidized to 8-oxo-6-carboxamidopurines **13** in solution. The mechanism of these reactions could follow the pathway outlined in Scheme 2 or that demonstrated in Scheme 4 and both appear equally plausible.

It will be recalled that pathway **B** (Scheme 1) proposed by Ohtsuka[7] suggested that the first intermediate formed was a Schiff-base derivative **5**, which then reacted with the isocyanate. It was important, therefore, to establish whether **5** could also be a precursor to compounds **12** and **13**. Reaction between DAMN and benzaldehyde gave **5** ($R^1 =$ Ph, $R^2 =$ H) in 98% yield (Scheme 5). On further reaction of this compound with phenyl isocyanate in acetonitrile in the presence of triethylamine, a white solid was obtained in 93% yield. According to Ohtsuka,[7] this compound should have the pyrimidine structure **8** ($R^1 = R^3 =$ Ph, $R^2 =$ H), although the evidence was based only on elemental analysis and IR spectroscopic data [ν (C≡N) 2200 cm^{-1} and strong absorptions at 1740 and 1630 cm^{-1}]. We now believe that this compound has structure **20** (Scheme 5). Compound **20** is an isomer of **8** and is indistinguishable from elemental analysis. The IR spectrum agrees with that reported by Ohtsuka.[7] Both the ^1H and ^{13}C NMR spectra in d_6-DMSO show two sets of bands indicative of isomers in the ratio of 3:1, which we believe correspond to the geometrical isomers **20A** and

Scheme 5



Compound	R^1	R^2	R^3	Reaction Conditions	Yield (%)	mp (°C)
5	Ph	H	-	2 h (rt)	98	
20	Ph	H	Ph	15 min (rt)	93	
22	Ph	-	Ph	96 h (rt)	24[a)]	

[a)] Solid suspension obtained from **20** and H_2O_2 in HOAc; compound **13a** was isolated from solution (32%)

20B, which are both stabilized by intramolecular hydrogen bonding. Interestingly, Ohtsuka also observed two sets of bands in the ^{1}H NMR spectrum of compound **8** (R^1 = 4-ClC_6H_4, R^2 = H, R^3 = Ph), but did not comment upon their significance.[7] Unfortunately, neither the ^{1}H nor the ^{13}C NMR spectral data are sufficient to prove the structure conclusively, the main features being the imine C−H, the imine N−H and the imidazole N−H at δ 8.78, 8.52, and 11.91, respectively, for isomer **A**, and at δ 8.93, 8.56, and 12.06, respectively, for isomer **B.** In the ^{13}C NMR spectrum a DEPT experiment has established the imine carbon atom at δ 158.35 for isomer **A** and at δ 159.36 ppm for isomer **B**. The main evidence for structure **20** is that on standing in a solution of DMSO-d_6 for 46 h at room temperature the spectrum changes and two clear doublets appear in the ^{1}H NMR spectrum at δ 6.01 (J = 6 Hz, 1H) identified as an NH proton by exchange with D_2O and at δ 5.76 ppm (J = 6 Hz, 1H) identified as a CH proton. We tentatively assign this new compound as **21** on the basis that the CH is now sp^3 and coupling between the adjacent protons (CH and NH) is observed. When a suspension of **20** in acetic acid and hydrogen peroxide was stirred at room temperature for 4 days it gave a low yield (19%) of a white solid believed to be the purine-6-carbonitrile **22**. The IR spectrum for this compound shows a weak ν (C≡N) absorption at 2254 cm^{-1} and an intense absorption at 1750 cm^{-1} for a C=O group. An absorption of medium intensity at 3228 cm^{-1} is indicative of a single NH, which appears in the ^{1}H NMR spectrum as a singlet at δ 12.95 ppm. The presence of a cyano group is confirmed by a signal at δ114.58 ppm in the ^{13}C NMR spectrum. After a further 3 days in DMSO-d_6, signals for the known 6-carboxamidopurine **13a** started to appear. This product was isolated and shown to be identical in all respects to the product isolated earlier by heating **12b** in ethanol, and this establishes beyond doubt the reactions outlined in Scheme 5.

In conclusion, this present investigation has demonstrated that the previously reported reactions of urea derivatives of DAMN with carbonyl compounds in the presence of triethylamine do not give pyrimidino[5,4-*d*]-pyrimidines by a mechanism involving rotation about the C=C bond. Instead, these reactions give the isomeric 8-oxo-6-carboxamido-1,2-dihydropurines and 8-oxo-6-carboxamidopurines (in the case of aldehyde precursors) by a mechanism that may involve initial cyclization to 2-oxoimidazole intermediates.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer, ^{1}H and ^{13}C NMR spectra on a Varian Unity Plus spectrometer. Mass spectra were recorded on a GC−MS Automass 120 or on a Kratos Concept instrument.

***N*-(2-Amino-1,2-dicyanovinyl)-*N'*-phenylurea (2a).** A solution of DAMN (0.60 g, 5.55 mmol) in dry acetonitrile (10 mL) was kept stirring in an ice bath, under a nitrogen atmosphere, in a round-bottom flask equipped with a serum cap. Phenyl isocyanate (0.70 g, 5.88 mmol) was added dropwise with a syringe through the serum cap, and 10 min later a precipitate started to appear. The mixture was stirred at room temperature for 24 h, when the cream solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as the title compound (1.19 g, 5.24 mmol, 95%). Characterization: mp 180−185 °C dec (lit.[1b] mp 180−210 °C dec); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.80 (s, 1 H), 7.54 (s, 1 H), 7.42 (d, J = 7.5 Hz, 2 H), 7.26 (t, J = 7.5 Hz, 2 H), 7.18 (s, 2 H), 6.97 (t, J = 7.5 Hz, 1 H); IR (Nujol mull) 2247 (m, CN), 2209 (s, CN), 1635 (s, C=O).

***N*-(2-Amino-1,2-dicyanovinyl)-*N'*-benzylurea (2b).** Benzyl isocyanate (0.65 g, 4.9 mmol) was added with a syringe to a suspension of diaminomaleonitrile (0.48 g, 4.40 mmol) in dry acetonitrile (5 mL), kept stirring under a nitrogen atmosphere in an ice bath. A homogeneous solution was formed after 30 min, and after another 20 min a white solid started to precipitate out of solution. After 17 h at 4 °C, the solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as the title compound (0.86 g, 3.60 mmol, 82%). Characterization: mp above 173 °C dec; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.52 (s, 1 H), 7.40−7.20 (m, 5 H), 7.04 (s, 2 H), 6.95 (t, J = 6.0 Hz, 1 H), 4.23 (d, J = 6.0 Hz, 2 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.8, 140.0, 128.2, 127.1, 126.7, 126.0, 117.3, 114.4, 91.4, 43.1; IR (Nujol mull) 2249 (w, CN), 2205 (s, CN), 1644 (s, C=O); MS (EI, 70 eV) m/z (rel int) 241 (M^+, 90). Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.75; H, 4.56; N, 29.05. Found: C, 59.81; H, 4.81; N, 28.72.

2,2-Dimethyl-8-oxo-9-phenyl-1,2-dihydropurine-6-carboxamide (12a). Triethylamine (50 μL) was added to a suspension of diaminomaleonitrile urea **2a** (0.15 g, 0.66 mmol) in acetone (20 mL), and the reaction mixture was stirred at room temperature. A solid precipitate started to develop after 3 h, and the reaction mixture was stirred for another 21 h. The solid was filtered and washed with acetone and diethyl ether to give the title compound (0.12 g, 0.42 mmol, 64%) as a cream solid. Characterization: mp 236−237 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.75 (s, 1 H), 7.61 (s, 1 H), 7.50−7.40 (m, 6 H), 4.97 (s, 1 H), 1.31 (s, 6 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.2, 154.0, 151.2, 133.7, 128.5, 126.7, 126.3, 119.6, 109.6, 70.1, 28.8; IR (Nujol mull) 1730 (s, C=O), 1713 (s, C=O), 1668 (s), 1641 (s). Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.29; N, 24.55. Found: C, 58.57; H, 5.22; N, 24.29.

2-(4'-Methoxyphenyl)-8-oxo-9-phenyl-1,2-dihydropurine-6-carboxamide (12b). Triethylamine (0.1 mL) was added to a suspension of diaminomaleonitrile urea **2a** (0.25 g, 1.01 mmol) and anisaldehyde (0.28 g, 2.05 mmol) in methanol (20 mL). The solution was stirred at room temperature, and 10 min later, a solid precipitate started to form. Stirring was continued for another 19 h at room temperature, when the solid was filtered and washed with ethanol and diethyl ether to give the title compound (0.30 g, 0.83 mmol, 82%) as a off-white solid. Characterization: mp 330−331 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.85 (s, 1 H), 7.53 (d, J = 8.5 Hz, 2 H), 7.42 (t, J = 9.0 Hz, 2 H), 7.32 (t, J = 9.0 Hz, 1 H), 6.90 (d, J = 9.0 Hz, 2 H) 5.67 (d, J = 4.5 Hz, 1H), 5.34 (d, J = 4.5 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.1, 158.9, 154.0, 153.1, 134.6, 133.5, 128.6, 128.1, 126.9, 126.2, 121.5, 113.4, 112.0, 69.7, 51.1; IR (Nujol mull) 1745 (s, C═O), 1697 (s, C═O). Anal. Calcd for $C_{19}H_{17}N_5O_3$: C, 62.80; H, 4.72; N, 19.27. Found: C, 62.51; H, 4.55; N, 19.30.

2,2-Tetrahydrothiopyranyl-8-oxo-9-phenyl-1,2-dihydropurine-6-carboxamide (12c). Triethylamine (0.1 mL) was added to a suspension of diaminomaleonitrile urea **2a** (0.23 g, 1.01 mmol) and thiopyranone (0.13 g, 1.12 mmol) in methanol (20 mL). The solution was stirred at room temperature, and 30 min later, a solid precipitate started to form. Stirring was continued for another 19 h at room temperature, when the solid was filtered and washed with methanol and diethyl ether to give the title compound (0.18 g, 0.55 mmol, 50%) as a cream solid. Characterization: mp 252−253 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.87 (s, 1 H), 7.63 (s, 1H), 7.54 (s, 1 H) 7.31 (t, J = 6.6 Hz, 1 H), 7.50−7.42 (m, 4 H), 4.61 (s, 1 H), 2.79−2.59 (m, 4 H), 2.00−1.91 (m, 4 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.6, 154.1, 151.1, 133.6, 128.6, 126.8, 126.1, 117.9, 111.7, 70.2, 37.3, 23.4; IR (Nujol mull) 1735 (s, C═O), 1713 (s, C═O), 1668 (s), 1642 (s). Anal. Calcd for $C_{16}H_{17}N_5O_2S\cdot 0.2\ H_2O$: C, 55.38; H, 4.94; N, 20.18; S, 9.24. Found: C, 55.24; H, 4.97; N, 19.94; S, 9.37.

2,2-Cyclohexanyl-8-oxo-9-phenyl-1,2-dihydropurine-6-carboxamide (12d). Triethylamine (0.1 mL) was added to a suspension of diaminomaleonitrile urea **2a** (0.30 g, 1.30 mmol) in cyclohexanone (10 mL), and the solution was stirred at room temperature. A solid precipitate started to be formed after 10 min, and stirring was continued for another 19 h. The solid was filtered and washed with diethyl ether to give the title compound (0.27 g, 0.83 mmol, 64%) as a cream solid. Characterization: mp 218−219 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.78 (brs, 1 H), 7.61 (s, 1 H), 7.50−7.39 (m, 5 H), 7.29 (t, J = 6.9 Hz, 1 H), 4.51 (s, 1 H), 1.80−1.30 (m 5 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.8, 154.2, 151.0, 133.8, 128.7, 126.8, 126.1, 118.4, 111.5, 71.4, 41.5, 36.9, 26.6, 25.5, 24.4; IR (Nujol mull) 1738 (s, C═O), 1715 (s, C═O), 1670 (s), 1645 (s). Anal. Calcd for $C_{17}H_{19}N_5O_2\cdot 0.2\ H_2O$: C, 62.07; H, 5.82; N, 21.29. Found: C, 62.49; H, 6.01; N, 20.91.

2,9-Diphenyl-8-oxopurine-6-carboxamide (13a). Triethylamine (0.1 mL) was added to a suspension of diaminomaleonitrile urea **2a** (0.25 g, 1.01 mmol) and benzaldehyde (0.23 g, 2.20 mmol) in methanol (20 mL), and the solution was stirred at room temperature. A solid precipitate started to be formed after 30 min, and stirring was continued for another 30 min. The solid was filtered and washed with diethyl ether to give the title compound (0.25 g, 0.75 mmol, 68%) as a pale yellow solid. Characterization: mp 323−324 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.80 (s, 1 H), 8.50 (s, 1 H), 8.45−8.42 (m, 2 H), 7.98 (s, 1 H), 7.71 (d, J = 7.8 Hz, 2 H), 7.60 (t, J = 8.1 Hz, 2 H), 7.47 (t, J = 7.8 Hz, 1 H), 7.46−7.44 (m, 3 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.6, 154.6, 152.87, 152.85, 136.8, 132.9, 132.7, 130.1, 129.0, 128.5, 127.9, 127.6, 126.4, 119.9; IR (Nujol mull) 1753 (s, C═O), 1702 (s, C═O). Anal. Calcd for $C_{18}H_{13}N_5O_2$: C, 65.25; H, 3.95; N, 21.14. Found: C, 65.01; H, 4.06; N, 21.15.

2-(4′-Methoxyphenyl)-9-phenyl-8-oxopurine-6-carboxamide (13b). Method A. A suspension of the corresponding 1,2-dihydropurine **12a** (0.10 g, 0.27 mmol) in ethanol (6 mL) was refluxed for 1 h. The reaction mixture was cooled to room temperature, leading to a white solid that was filtered and washed with cold ethanol. The product was identified as the title compound (0.01 g). A second crop was obtained concentrating the mother liquour in the rotary evaporator, and the solid which was filtered and washed with cold ethanol was identical to the product isolated in the first crop, giving a total of 0.04 g (0.11 mmol, 41%). Characterization: mp 330−332 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.70 (s, 1 H), 8.49 (s, 1 H), 8.37 (d, J = 9.3 Hz, 2 H), 7.96 (s, 1 H), 7.71 (d, J = 7.2 Hz, 2 H), 7.60 (t, J = 7.5 Hz, 2 H), 7.47 (t, J = 7.2 Hz, 1 H), 6.98 (d, J = 9.3 Hz, 2 H), 3.80 (s, 3 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.7, 161.0, 154.7, 152.9, 152.8, 133.0, 132.7, 129.4, 129.2, 128.9, 127.8, 126.3, 119.3, 113.8, 55.3; IR (Nujol mull) 1745 (s, C═O), 1696 (s, C═O). Anal. Calcd for $C_{19}H_{15}N_5O_3\cdot 0.2\ H_2O$: C, 62.53; H, 4.14; N, 19.19. Found: C, 62.46; H, 4.25; N, 19.06.

Method B. A suspension of diaminomaleonitrile urea **2a** (0.20 g, 0.88 mmol) in dry acetonitrile (8 mL) was stirred in an ice bath. Addition of DBU (three drops) caused the white suspension to evolve to a dark yellow suspension, which was stirred in the ice bath for 2 h. A brown solution was formed and was stirred for a further 19 h at 4 °C. The dark suspension was removed by filtration, and anisaldehyde (0.23 g, 1.70 mmol) was added to the clear, brown solution. An orange precipitate had been formed after 25 min at room temperature, and the mixture was stirred for a further 6 h. The solid was filtered and washed with acetonitrile to give the title compound (0.15 g, 0.42 mmol, 47%) as an orange solid.

2-(4′-Cyanophenyl)-9-phenyl-8-oxopurine-6-carboxamide (13c). Triethylamine (0.1 mL) was added to a suspension of diaminomaleonitrile urea **2a** (0.23 g, 1.01 mmol) and 4-cyanobenzaldehyde (0.26 g, 1.98 mmol) in methanol (20 mL). The solution was stirred at room temperature, and after 15 min, a solid precipitate started to develop. The mixture was stirred for another 18 h, when the product was filtered and washed with methanol and diethyl ether to give the title compound (0.25 g, 0.70 mmol, 69%) as a cream solid. Characterization: mp above 340 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.90 (s, 1 H), 8.63 (s, 1 H), 8.61 (d, J = 8.1 Hz, 2 H), 8.01 (s, 1 H), 7.92 (d, J = 8.1 Hz, 2 H), 7.70 (d, J = 7.8 Hz, 2 H), 7.61 (t, J = 8.4 Hz, 2 H), 7.48 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.4, 152.97, 152.94, 152.7, 141.0, 132.9, 132.5, 129.1, 128.2, 128.1, 126.4, 120.7, 118.9, 112.2; IR (Nujol mull) 2229 (m, CN), 1754 (s, C═O), 1685 (s, C═O).

2-(4′-Nitrophenyl)-9-phenyl-8-oxopurine-6-carboxamide (13d). Triethylamine (0.1 mL) was added to a suspension of diaminomaleonitrile urea **2a** (0.18 g, 0.80 mmol) and 4-nitrobenzaldehyde (0.19 g, 1.25 mmol) in methanol (20 mL). The solution was stirred at room temperature, and after 5 min, a yellow/orange solid precipitate started to develop. The mixture was stirred for another 18 h, when the product was filtered and washed with methanol and diethyl ether to give the title compound (0.27 g, 0.72 mmol, 90%) as a greenish yellow solid. Characterization: mp 218−220 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.97 (s, 1 H), 8.65 (d, J = 8.7 Hz, 2 H), 8.61 (s, 1 H), 8.26 (d, J = 9.0 Hz, 2 H), 8.02 (s, 1H), 7.69 (d, J = 8.4 Hz, 2 H), 7.60 (t, J = 7.2 Hz, 2 H), 7.49 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.4, 153.02, 152.95, 152.3, 148.3, 142.8, 132.9, 132.5, 129.1, 128.7, 128.1, 126.5, 123.7, 120.9; IR (Nujol mull) 1754 (s, C═O), 1684 (s, C═O). Anal. Calcd for $C_{18}H_{12}N_6O_4$: C, 57.45; H, 3.21. Found: C, 57.32; H, 3.51.

2-Methyl-9-phenyl-8-oxopurine-6-carboxamide (13e). Triethylamine (0.1 mL) was added to a suspension of diaminomaleonitrile urea **2a** (0.23 g, 1.01 mmol) in acetylacetone (10 mL), and the mixture was stirred at room temperature. After 10 min a solid precipitate started to develop and stirring was continued for another 19 h. The product was filtered and washed with methanol and diethyl ether to give the title compound (0.21 g, 0.78 mmol, 78%) as a white solid. Characterization: mp 310 °C dec; Anal. Calcd for $C_{13}H_{11}N_5O_2$: C, 57.99; H, 4.12; N, 26.01. Found: C, 57.85; H, 4.29; N, 25.87; IR (Nujol mull) 1750 (s, C═O), 1703 (s, C═O). The ^{1}H and ^{13}C NMR spectra of compound **13e** could not be obtained due to the poor solubility of this compound in DMSO-d_6.

2-(4′-Methoxyphenyl)-9-benzyl-8-oxopurine-6-carboxamide (13f). Method A. Anisaldehyde (0.08 g, 0.58 mmol) was added to a suspension of diaminomaleonitrile urea **2b** (0.07 g, 0.28 mmol) in ethanol (5 mL) kept stirring at room temperature. Triethylamine (0.03 g, 0.29 mmol) was added to the reaction mixture after 10 min. A homogeneous solution was obtained after 3 h at room temperature, and shortly after a white solid started to precipitate out. After 18 h, TLC indicated that the reaction was almost complete. The solid was filtered after another 2 days, washed with ethanol and diethyl ether and identified as the title compound (0.07 g, 0.20 mmol, 70%). Characterization: mp above 300 °C dec; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.60 (brs, 1 H), 8.47 (d, $J = 8.7$ Hz, 2 H), 8.44 (brs, 1 H), 7.92 (brs, 1 H), 7.40−7.20 (m, 5 H), 7.02 (d, $J = 8.7$ Hz, 2 H), 5.08 (s, 2 H), 3.82 (s, 2 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.6, 161.0, 154.7, 153.7, 152.8, 136.5, 132.7, 129.5, 129.3, 128.6, 127.8, 127.6, 119.2, 113.8, 55.3, 42.7; IR (Nujol mull) 1723 (s, C═O), 1665 (s, C═O). Anal. Calcd for $C_{20}H_{17}N_5O_3$: C, 64.00; H, 4.53; N, 18.67. Found: C, 63.63; H, 4.58; N, 18.52.

Method B. Anisaldehyde (0.10 g, 0.74 mmol) was added to a suspension of **19b** (0.06 g, 0.23 mmol) in ethanol (10 mL), and the mixture was stirred at room temperature for 18 h. A new white solid had been formed in a yellow/orange solution, and the mixture was stirred at room temperature for another 2 days. The solid was filtered and washed with ethanol and diethyl ether. The product was identified as the title compound (0.05 g, 0.13 mmol, 58%).

5-Amino-1-benzyl-4-cyanoformimidoyl-imidazole-2-one (19). A catalytic amount of DBU (70 μL) was added to a suspension of diaminomaleonitrile urea **2b** (0.15 g, 0.62 mmol) in dry acetonitrile (2 mL), and the mixture was stirred at 4 °C for 18 h, when the TLC indicated that the reaction was complete. The yellow solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as the title compound (0.11 g, 0.46 mmol, 74%). Characterization of imidazole **19**, present in the NMR spectra as two isomeric forms **A** and **B**, in a 2:1 ratio: mp above 175 °C dec; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.15 (brs, 2 H, **A** + **B**), 8.02 (s, 1 H, **B**), 7.83 (s, 1 H, **A**), 7.35−7.20 (m, 5 H, **A** + **B**), 5.61 (s, 2 H, **A**), 5.35 (s, 2 H, **B**), 4.72 (s, 2 H, **B**), 4.68 (s, 2 H, **A**); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 153.9 (**B**), 153.7 (**B**), 153.6 (**A**), 153.0 (**A**), 150.5 (**B**), 137.1 (**B**), 136.6 (**A**), 128.5 (**B**), 128.4 (**A**), 127.4 (**B**), 127.3 (**B**), 118.0 (**B**), 116.2 (**A**), 116.0 (**A**), 114.5 (**A**), 99.3 (**A**), 41.4 (**A**), 40.5 (**B**); IR (Nujol mull) 2210 (m, CN), 1758 (m, C═O); MS (EI, 70 eV) *m*/*z* (rel int) 241 (M$^+$, 40). Anal. Calcd for $C_{12}H_{11}N_5O$; C, 59.75; H, 4.56; N, 29.05. Found: C, 59.62; H, 4.81; N, 28.75.

1-Benzylideneamino-2-amino-1,2-dicyanoethylene (5). Benzaldehyde (0.20 g, 1.88 mmol) was added to a solution of DAMN (0.20 g, 1.85 mmol) and concentrated sulfuric acid (3 drops) in dimethyldulfoxide (25 mL). The mixture was stirred at room temperature for 15 min and poured into an ice/water bath (250 mL). After 2 h, the solid was filtered and washed with water to give the title compound (0.36 g, 1.80 mmol, 98%) as a pale yellow solid. Characterization: mp 206−208 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.26 (s, 1 H), 8.00−8.05 (m, 2 H), 7.94 (s, 2 H), 7.50−7.40 (m, 3 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.1, 135.5, 131.5, 129.0, 128.7, 127.0, 126.9, 114.3, 113.7, 102.6; IR (Nujol mull) 2239 (m, CN), 2204 (s, CN), 1608 (s), 1579 (s).

Reaction of 1-Benzylideneamino-2-amino-1,2-dicyanoethylene 5 with Phenyl Isocyanate. Triethylamine (3 drops) was added to a suspension of 1-benzylideneamino-2-amino-1,2-dicyanoethylene **5** (1.00 g, 5.10 mmol) and phenyl isocyanate (0.70 g, 5.88 mmol) in acetonitrile (20 mL). The reaction mixture was warmed gently in a water bath, and after 15 min, the white precipitate that had been formed was filtered and washed with acetonitrile. The product was identified as the substituted imidazole **20** (1.49 g, 4.73 mmol, 93%). Characterization of imidazole **20**, present in the NMR specta as two isomeric forms **A** and **B**, in a 3:1 ratio: mp 241−242 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.06 (s, 1 H, B), 11.91 (s, 1 H, A), 8.93 (s, 1 H, B), 8.78 (s, 1 H, A), 8.56 (s, 1 H, B), 8.52 (s, 1 H, A), 8.19 (d, $J = 6.9$ Hz, 2 H, A+B), 7.60−7.39 (m, 8 H, A+B); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 159.4 (B), 158.4 (A), 152.7 (B), 152.4 (A), 151.9 (B), 150.6 (A), 139.8, 136.2 (B), 135.4 (A), 130.9, 129.7, 129.5, 128.9, 128.7, 128.1, 127.9, 112.1, 98.7; IR (Nujol mull) 2210 (m, CN), 1736 (s, C═O). Anal. Calcd for $C_{18}H_{13}N_5O$: C, 68.56; H, 4.16; N, 22.21. Found: C, 68.53; H, 4.03; N, 22.29.

Cyclization of Imidazole 20 in Acetic Acid and Hydrogen Peroxide. A suspension of imidazole **20** (0.20 g, 0.66 mmol) in acetic acid (8 mL) and hydrogen peroxide 30% (2 mL) was stirred at room temperature for 4 days. The pale yellow suspension evolved to a white solid, which was filtered and washed with ethanol and diethyl ether. This product was identified as the 6-cyanopurine **22** (0.05 g, 0.16 mmol, 24%). Characterization: mp 289−291 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.94 (brs, 1 H), 8.21−8.17 (m, 2 H), 7.71−7.47 (m, 8 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.2, 152.7, 136.3, 132.1, 130.7, 129.2, 128.8, 128.4, 127.2, 126.3, 125.3, 114.7, 113.9; IR (Nujol mull) 2254 (w, CN), 1751 (s, C═O). The mother liquour was neutralized by ammonium hydroxide leading to a white precipitate which was filtered and washed with water and diethyl ether. This product was identified as the 8-oxopurine-6-carboxamide **13a** (0.07 g, 0.21 mmol, 32%).

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