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Efficient Synthesis of 3*H*-Imidazo[4,5-*b*]pyridines from Malononitrile and 5-Amino-4-(cyanoformimidoyl)imidazoles

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1-Aryl-5-amino-4-(cyanoformimidoyl)imidazoles **2** were reacted with malononitrile under mild experimental conditions and led to 3-aryl-5,7-diamino-6-cyano-3*H*-imidazo[4,5-*b*]pyridines **5**, when the reaction was carried out in the presence of DBU, or to 3-aryl-5-amino-6,7-dicyano-3*H*-imidazo-[4,5-*b*]pyridines **3**, in its absence. Both reactions evolved from the adduct formed by nucleophilic attack of the malononitrile anion to the carbon of the cyanoformimidoyl substituent. A 5-amino-1-aryl-4-(1-amino-2,2-dicyanovinyl)imidazole **4** was isolated when this reaction was carried out in the presence of DBU. The structure of compound **4** was confirmed by spectroscopic methods and by reaction with triethyl orthoformate and with acetic anhydride, leading respectively to 9-aryl-6-(cyanomethylidene)purines **11** and **12**. Imidazole **2b** was also reacted with ethyl acetoacetate, a carbon acid with a pK_a comparable to that of malononitrile. Similar reaction conditions were used and the product isolated was a 6-carbamoyl-1,2-dihydropurine **10**, showing that a different mechanism was operating in this case.

Introduction

Compounds incorporating the imidazo[4,5-*b*]pyridine ring system can be considered structural analogues of purines and have shown a diverse biological activity, depending on the substituents of the heterocyclic ring. Their activity includes anticancer,[1] antiviral,[2] antimitotic,[3] and tuberculostatic[4] action. They have also been evaluated as antagonists of various biological receptors including angiotensin II,[5] and thromboxane A_2.[6] Appropriately substituted imidazo[4,5-*b*]pyridines have also displayed high affinity for A_1 adenosine receptors.[7]

Most of the synthetic methods that were used for the preparation of imidazo[4,5-*b*]pyridines generate the imidazole ring from a substituted pyridine, under suitable reaction conditions.[1a,3,8] Examples where the pyridine ring is built from a conveniently substituted imidazole[7c,9] are not as common.

In our research group, we have been interested in studying the reactivity of 5-amino-4-(cyanoformimidoyl)-imidazoles **2**, easily prepared by base-catalyzed cyclization of *Z*-(*N*)-2-amino-1,2-dicyanovinyl formamidines.[10,11] These substituted imidazoles are versatile precursors of fused nitrogen heterocycles, especially the purine ring. The synthesis of 6-carbamoyl-,[11] 6-cyano-,[11c,12] 6-alkoxy-,[12] and 6-amidinopurines[13] has been previously reported, and all the reactions are initiated at the

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cyanoformimidoyl unit in the 4-position of the imidazole ring. This work reports the efficient synthesis of functionalized imidazo[4,5-*b*]pyridines, isolated when malononitrile is combined with *N*-aryl-5-amino-4-(cyanoformimidoyl)imidazoles.

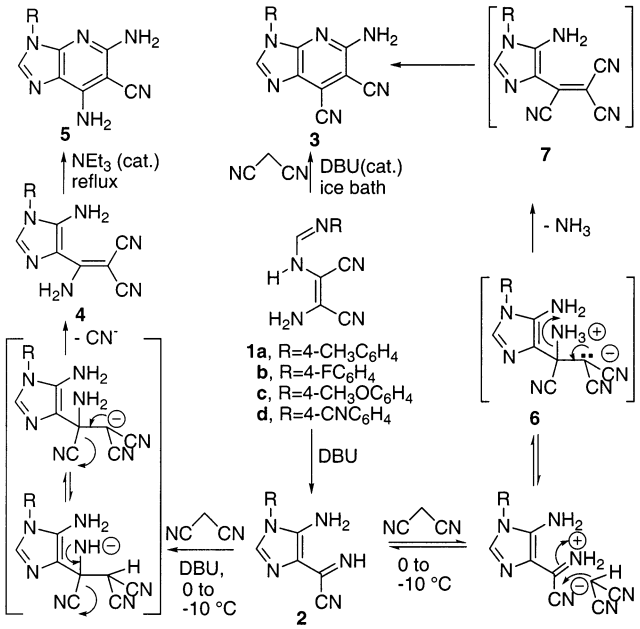
Results and Discussion

Addition of malononitrile (approximately 1.5 molar equiv) to a suspension of 5-amino-4-(cyanoformimidoyl)-imidazoles **2a** or **2b** in acetonitrile and stirring the reaction mixture in an ice bath for 5 h followed by 2 days at −10 °C led to the formation of a yellow solid identified as the 3*H*-imidazo[4,5-*b*]pyridine **3a** and **3b** (Scheme 1). These products were isolated in 91 and 93% yield, respectively. When the same reaction was carried out from imidazoles **2c** and **2d**, the poor solubility of these compounds in acetonitrile required the addition of DMF (1:1 volume ratio). The reaction occurred under similar experimental conditions, leading selectively to the formation of compounds **3c** (90%) and **3d** (98%). The best experimental conditions were those where the ammonia evolved during the reaction was kept in solution until all the starting material was consumed. When the serum cap was removed at regular intervals (to follow the reaction by TLC), lower yields were obtained for the imidazopyridine (75−78%), suggesting that the cyclization reaction is base-catalyzed.

The reaction of malononitrile and 5-amino-4-(cyanoformimidoyl)imidazole was repeated in the presence of DBU (approximately 1.2 molar equiv) using ethanol (**2b**), ethanol/acetonitrile (**2a**), or ethanol/DMF (**2c**) as solvent mixtures, and the product isolated after 3−4 days at −10 °C was identified as imidazole **4**. Compounds **4a**−**c** were isolated in 93−95% yield. Compound **4d** could not be isolated under similar experimental conditions, as it readily cyclizes to give the corresponding *3H*-imidazo-[4,5-*b*]pyridine **5d**, isolated as a white solid in 69% yield. The analogous imidazo[4,5-*b*]pyridines **5a**−**c** were prepared by intramolecular cyclization of 5-amino-1-aryl-4-(1′-amino-2′,2′-dicyanovinyl)imidazoles **4**. This reaction occurred when compounds **4a** and **4b** were refluxed in ethanol for 2 h, in the presence of a catalytic amount of triethylamine. These experimental conditions could not be used for imidazole **4c**, due to its low solubility in ethanol. In this case, only the starting material was quantitatively recovered after a 2-h reflux period. When a suspension of **4c** in a mixture of ethanol:DMF (3:2) and DBU (1.4 molar equivalents) was refluxed for 40 h, a white solid, identified as **5c**, was isolated in 80% yield.

To understand the mechanism for both reactions, imidazole **2a** (0.045 mmol) was combined with 1 equiv of malononitrile in deuterated acetonitrile (700 μL), and the reaction was followed by ^{1}H NMR at 24 °C. A yellow color rapidly developed in solution, which was considered an indication that a low concentration of the malononitrile anion had been formed. A fast reaction occurred, as after 40 min at 24 °C, a considerable amount of imidazopyridine **3a** precipitated out of solution, preventing the registration of further spectra. The only compounds detected in the reaction mixture were **2a**, **7a**, and **3a**.

SCHEME 1



Compound	R	Reaction Conditions	Yield (%)
3a	4-MeC$_6$H$_4$	ethanol; DBU (cat.) 4h (0 °C); 1 day (-10 °C)	90[a]
		acetonitrile 5 h (0 °C); 2 days (-10 °C)	91
3b	4-FC$_6$H$_4$	acetonitrile 5 h (0 °C); 2 days (-10 °C)	93
3c	4-MeOC$_6$H$_4$	acetonitrile:DMF (1:1) 5 h (0 °C); 2 days (-10 °C)	90
3d	4-CNC$_6$H$_4$	acetonitrile:DMF (1:1) 5 h (0 °C); 10 days (-10 °C)	98
4a	4-MeC$_6$H$_4$	Ethanol:acetonitrile (6:1); DBU 5 h (0 °C); 4 days (-10 °C)	95
4b	4-FC$_6$H$_4$	Ethanol; DBU 5 h (0 °C); 3 days (-10 °C)	93
4c	4-MeOC$_6$H$_4$	Ethanol:DMF (3:2); DBU 5 h (0 °C); 3 days (-10 °C)	95
5a	4-MeC$_6$H$_4$	Ethanol; NEt$_3$ 2 h (reflux)	40
5b	4-FC$_6$H$_4$	Ethanol; NEt$_3$ 2 h (reflux)	80
5c	4-MeOC$_6$H$_4$	DMF; DBU 40 h (reflux)	80
5d	4-CNC$_6$H$_4$	Ethanol; DBU 5 h (0 °C); 20 days (-10 °C)	69

[a] Yield and reaction conditions from amidine **1a**. All the other yields and experimental conditions correspond to reactions where imidazole **2** was used as starting material.

When malononitrile (0.045 mmol) was combined with 1 equiv of DBU (ca. 7 μL) in deuterated acetonitrile (700 μL) and the imidazole **2a** (0.045 mmol) was added to the pale yellow solution, a much slower reaction occurred. After 40 min at 24 °C, only traces of products **4a**, **5a**, and 5-amino-4-cyano-1-(4′-tolyl)imidazole were detected in solution, which was gradually becoming pale brown. After 22 h at 24 °C, the major product was 5-amino-4-cyano-1-(4′-tolyl)imidazole (71% of the reaction mixture). Under these experimental conditions, the concentration of malononitrile anion is higher, but the added base (DBU) competes for the elimination of HCN from the 5-amino-4-cyanoformimidoylimidazole **2a**. This situation

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has been previously reported to occur with other bases (usually NaOH).[10b,11a,b]

^{1}H NMR was also used to confirm the elimination of HCN by addition of DBU to imidazole **2a**. When these compounds (**2a**:DBU, 1:3 molar ratio) were combined in deuterated acetonitrile and the ^{1}H NMR spectrum was run after 3 h at 24 °C, the only compounds detected in solution were 5-amino-4-cyanoimidazole and the starting material **2a** (7:3 ratio).

This study led us to consider for these reactions a mechanism where the malononitrile anion is the nucleophile in both cases (Scheme 1). In the presence of an excess of a strong base (DBU), a high concentration of the malononitrile anion is formed and reaction with imidazole **2** leads to a stabilized carbanion, which promptly evolves to the alkene by elimination of the cyanide ion, leading to **4**. When no other base is added, imidazole **2** may act as a mild base, and the positive charge generated in this molecule accelerates the nucleophilic attack by the malononitrile anion, even if its concentration in solution is low. In this case, elimination of ammonia is responsible for the formation of intermediate **7**. This compound could not be isolated, as it remains in solution and readily cyclizes to give **3**.

The use of an excess of DBU as a base proved to be essential in order to generate selectively the imidazole **4** and consequently the imidazo[4,5-*b*]pyridine **5**. The reaction mixture has to be kept at 0 to −10 °C, as these experimental conditions considerably reduced the competitive formation of 5-amino-4-cyanoimidazole. A number of reactions were carried out using triethylamine as base and imidazoles **2a** and **2b** as the starting material. Imidazole **2a** and malononitrile were combined in a 1:1.4 molar ratio using acetonitrile as solvent, and triethylamine (approximately 0.1 molar equivalents) was added to the reaction mixture (prepared in a 0.7 mmolar scale). The solid isolated after 5 days at −10 °C proved to be a mixture of compounds **3a** and **4a** in a 2:1 molar ratio, according to the ^{1}H NMR integration (75% crude yield). Similar experimental conditions were applied to the reaction of imidazole **2b** with malononitrile, and the solid isolated after 5 h at 0 °C was also a mixture of compounds **3b** and **4b** in a 2:1 molar ratio, by ^{1}H NMR (71% crude yield). When this reaction was repeated using triethylamine (approximately 1.5 molar equiv), the solid mixture isolated after 1 day at −10 °C showed that compounds **3b** and **4b** were formed in a 1:3 molar ratio (98% crude yield). Increasing the imidazole **2b**:malononitrile ratio to 1:2.5 with the same amount of triethylamine led to a reaction mixture where **3b** and **4b** were again present in a 1:3 molar ratio, after 1 day at −10 °C. Extensive darkening of the reaction mixture may be responsible for the lower isolated yield of the crude product (66%). These results indicate that the strength of the external base is crucial in order to get selective elimination of HCN from the adduct.

The amount of DBU that is used in this reaction (aproximately 1.2 equiv) is also important. When amidine **1a** was combined with a catalytic amount of DBU, cyclization to imidazole **2a** occurred promptly. A slight excess of malononitrile was added to the cold reaction mixture, and the imidazopyridine **3a** was isolated in 90% yield after 24 h. This indicates that the amount of DBU required to induce cyclization in amidine **1a** is not enough to generate a high concentration of the malononitrile anion responsible for the formation of **5**.

The structure of imidazopyridines **3** and **5** and imidazole **4** was confirmed by spectroscopic methods. For imidazole **4**, the two cyano groups are present in the IR spectrum as two distinct and intense bands in the 2203−2220 and 2182−2195 cm^{-1} region. In the ^{13}C NMR spectrum, the signals for both cyano groups are either absent or very weak bands around δ 112 and 114 ppm. Another typical feature is the chemical shift of both carbon atoms of the alkene substituent in the 4-position of the imidazole ring. The carbon atom directly bonded to the amino group gives a signal around δ 163 ppm, while the adjacent carbon (bonded to the two cyano groups) leads to a small band around δ 44 ppm. In the ^{1}H NMR spectrum, the two amino groups lead to two singlets (δ 5.0−5.8 and 7.7−8.0 ppm), each one integrating for two protons. The signal at δ 7.5 ppm for the C−H proton supports the presence of the imidazole ring. For imidazopyridines **3**, the IR spectrum shows the two cyano groups as a weak band around 2240 cm^{-1} and as a medium intensity band in the 2180−2230 cm^{-1} region. The presence of these two functional groups is confirmed in the ^{13}C NMR spectrum, as two peaks are always present around δ 115 and 113 ppm. The chemical shifts for C-5 ($\delta \approx$ 158 ppm), C-6 ($\delta \approx$ 87 ppm), and C-7 ($\delta \approx$ 114 ppm) are also typical of these compounds and reflect the effect of the substituent. A single amino group is now visible in the ^{1}H NMR spectrum as a singlet at δ 7.3−7.4 ppm, integrating for two protons. For imidazopyridines **5**, the IR spectrum shows a single intense band in the 1995−2200 cm^{-1} region, indicating that a single cyano group is present. This observation is confirmed by ^{13}C NMR, where a signal around δ 116 ppm can be assigned to this functional group. Another typical feature seems to be the chemical shift for C-5 ($\delta \approx$ 159 ppm), C-6 ($\delta \approx$ 70 ppm), and C-7 ($\delta \approx$ 147 ppm), reproducing the electronic effect of the amino and cyano substituents. The signal corresponding to C-6 is a very small peak in the spectra of both compounds **3** and **5**. The two amino groups are visible both in the IR and in the ^{1}H NMR spectra, which shows two singlets at δ 6.2−6.4 and 7.0−7.1 ppm, each one integrating for two protons.

Considering that the acidity of malononitrile (p$K_a \approx$ 11−12)[14] could be an important factor to the usefulness of this synthetic method for the preparation of highly functionalized imidazo[4,5-*b*]pyridines, a comparably acidic carbon acid was reacted with 5-amino-4-(cyanoformimidoyl)imidazole **2b**. Ethyl acetoacetate (p$K_a \approx$ 11)[14] and imidazole **2b** were combined in a 1.3:1 molar ratio, using acetonitrile as solvent, and the mixture was stirred at 0 °C for 3 h followed by 2 days at room temperature (Scheme 2). An orange suspension developed and the solid was identified as the 6-carbamoyl-1,2-dihydropurine **10** (43% yield), considering the typical spectroscopic features previously reported for this type of compounds.[10a,11,15] The use of a 3:1 mixture of acetonitrile and

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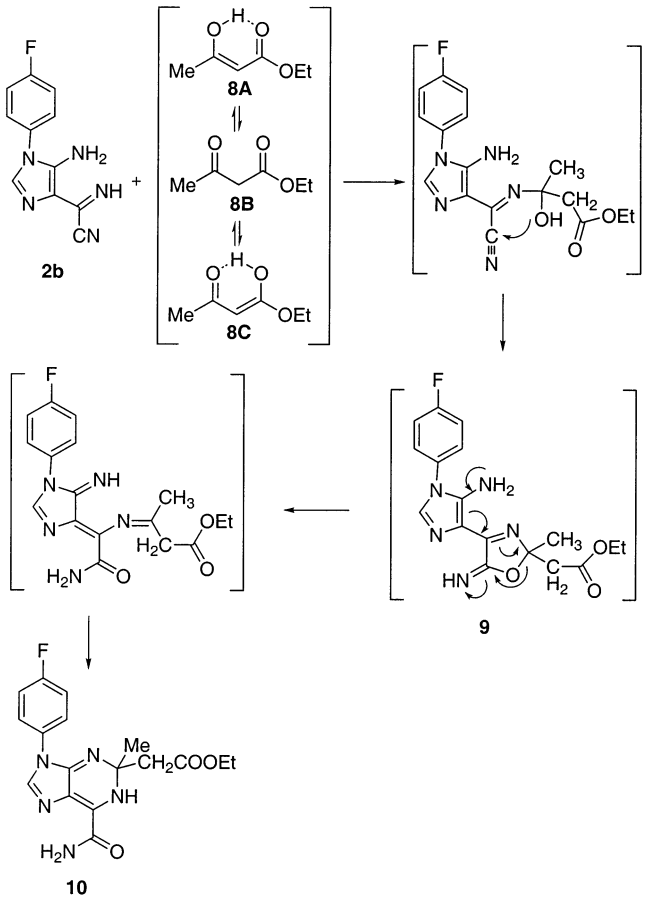
SCHEME 2



DMF as solvents and 4.5 molar equiv of ethyl acetoacetate improved the isolated yield of product **10** (76%). The same orange solid was isolated when the reaction was carried out in chloroform, in the presence of 7.5 molar equiv of ethyl acetoacetate, leading to purine **10** in 82% yield. In this case, a different reaction mechanism operates. This involves nucleophilic attack of the imine nitrogen to the more reactive carbonyl carbon atom of ethyl acetoacetate. The reaction proceeds with intramolecular hydrolysis of the adjacent cyano group, through an intermediate **9** that rapidly ring opens and cyclizes again by nucleophilic attack of the 5-amino group to the imine carbon atom. The formation of 1,2-dihydropurines of type **10** was previously reported[10a,11,15] and occurs when a 5-amino-4-(cyanoformimidoyl)imidazole **2** (R = alkyl, aryl, NHR′) reacts with an aldehyde or ketone. The mechanism for this reaction was confirmed with the isolation and characterization of an intermediate analogous to compound **9**.[16]

This reaction was also performed under the same experimental conditions that led to elimination of HCN from the adduct of **2** and malononitrile (ice bath and addition of 1.2 equiv of DBU). No evolution was detected by TLC after 4 h at 0 °C, and the reaction mixture was stirred at room temperature for a further 4 days. The small amount of solid suspension was filtered and identified as imidazole **2b** (10%). TLC on the pale orange

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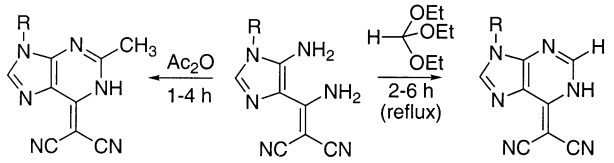
SCHEME 3



12 **4a**, R=4-$CH_3C_6H_4$ **b**, R=4-FC_6H_4 **11**

Compound	R	Reaction Conditions	Yield (%)
11a	4-MeC_6H_4	1.5 h (reflux)	77
11b	4-FC_6H_4	6 h (reflux)	78
12a	4-MeC_6H_4	4 h (reflux)	50
12b	4-FC_6H_4	1 h (reflux)	57

solution indicated the presence of a large amount of imidazole, a faint spot that could be assigned to the 1,2-dihydropurine, and two other minor contaminants. All attempts to isolate a pure product from the mother liquor failed, possibly because the solubility properties of these compounds were similar to those of DBU.

These results indicate that the acidity of the carbon acid is not the major factor controlling the reaction mechanism. It is possible that the highly stable enol forms **8A** and **8C** for ethyl acetoacetate greatly hinder the capacity of this compound to act as a carbon nucleophile through the anion of **8B**. Active methylene compounds stabilized by two adjacent carbonyl groups may behave in a similar way, but all the other active methylene compounds are expected to act as malononitrile in the reaction with 5-amino-4-(cyanoformimidoyl)imidazoles, leading to imidazo[4,5-*b*]pyridine structures.

Compounds **4a** and **4b** were used as precursors of 1,6-dihydropurines (Scheme 3) by reaction with triethyl orthoformate (leading to **11a** and **11b**) and with acetic anhydride (leading to **12a** and **12b**), under reflux conditions. A fast reaction occurs between both amine functions of imidazole **4** and the electrophilic reagent used as solvent, generating 9-aryl-6-(cyanomethylidene)purines **11** and **12**. The synthesis of 6-cyanomethylidene-9-substituted purines was previously reported by reaction of 6-chloropurine with malononitrile[17] or with the carbanion derived from malononitrile.[18] A similar reaction occurred when the anion of malononitrile was reacted with 6-methylsulfonylpurine.[19]

A detailed spectroscopic analysis carried out on purines **11** and **12** identifies the typical features associated with these structures. The two cyano groups are present in the IR spectrum as an intense band around 2214 cm^{-1} and a medium intensity band around 2190 cm^{-1}. These groups were visible only in the ^{13}C NMR spectrum of compounds **12a** and **12b**, as two distinct bands in the δ 117 ppm region. The identification of the ring carbon atoms was made on the basis of HMBC data for compound **11a**. The three-bond interaction of C2−H (δ 8.27

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ppm) identifies C6 (δ 151.9 ppm) and C4 (δ 146.6 ppm). The signals for C4 and C5 (δ 124.1 ppm) are also three-bonds away from C8−H (δ 8.70 ppm). The signal for the exocyclic double bond was absent in the ^{13}C NMR spectrum of compounds **11** and **12**. Another typical feature of these 1,6-dihydropurines is the chemical shift for the acidic N−H, in the ^{1}H NMR spectrum, identified as a very broad singlet in the δ 12.6−13.6 ppm region. The ^{1}H NMR spectra of compounds **12a** and **12b** show that these solids incorporate a small quantity of acetic acid (δ 2.1 or 1.9 ppm for the methyl group of the acid or its salt).[20] This observation is confirmed by elemental analysis, where calculations indicate the presence of 25% of acid.

Conclusion

The reaction of 5-amino-4-(cyanoformimidoyl)imidazoles **2** with malononitrile occurs selectively on the carbon of the cyanoformimidoyl substituent. Intramolecular cyclization of the adduct leads to 3*H*-imidazo[4,5-*b*]-pyridines **3** or **5**, depending on whether the reaction is carried out in the absence or in the presence of DBU, respectively.

When imidazole **2** was reacted with ethyl acetoacetate, the 6-carbamoyl-1,2-dihydropurine **10** was isolated, indicating that a different mechanism operates in this case. This reaction is much slower in the presence of an excess of DBU, as the starting material was identified as the major component of the reaction mixture after 4 h at 0 °C and 4 days at room temperature. Three minor products were also present in the reaction mixture, and one of them was identified as the 1,2-dihydropurine **10**. This result confirms that the preferred pathway in the reaction of imidazole **2** with active methylene compounds does not depend solely on the pK_a of the carbon acid. The possibility of generating stable enol forms may be responsible for the different chemical behavior of these 1,3-dicarbonyl compounds.

Imidazole **4**, generated from compound **2** and malononitrile upon elimination of hydrogen cyanide, is a good precursor of 6-(cyanomethylidene)purines **11** and **12** by reaction with triethyl orthoformate and acetic anhydride, respectively.

Experimental Section

The fluorine coupling constants in the ^{13}C NMR spectra were verified in all the samples using DEPT 45 (where the aromatic C−H signals were identified as doublets) and in some cases using the HMBC technique (to identify the signals for the aromatic C_i and C_p).

Safety. The reaction mixtures containing cyanide ion can be oxidized with calcium hypochlorite in basic solution, to the much less toxic cyanate ion, following the destruction procedure described in the literature.[21]

General Procedure for the Synthesis of 5-Amino-3-aryl-6,7-dicyano-3*H*-imidazo[4,5-*b*]pyridines (3). Malononitrile (0.04 g, 0.61 mmol) was added to a suspension of 5-amino-1-aryl-4-(cyanoformimidoyl)imidazoles **2** (0.41−0.44 mmol) in acetonitrile (5 mL) (for **3a** and **3b**) or acetonitrile and DMF in a 1:1 ratio (6 mL) (for **3c** and **3d**). The addition took place in an ice bath, and the mixture was stirred in ice for 5 h. The reaction mixture was allowed to stand at −10 °C for 2−10 days, when the solid was filtered and washed with diethyl ether.

Reaction of *Z*-(*N*)-2-amino-1,2-dicyanovinyl-(*N*′)-*p*-tolylformamidine 1a with Malononitrile. DBU (0.06 mmol) was added to a suspension of formamidine **1a** (0.10 g, 0.44 mmol) in ethanol (3 mL). The reaction mixture was stirred at room temperature for 5 min and then cooled in an ice bath before malononitrile (0.04 g, 0.61 mmol) was added. Stirring in the ice bath was continued for another 4 h and the mixture was allowed to stand at −10 °C for 24 h. The precipitate was filtered and washed with diethyl ether and the yellow solid was identified as compound **3a** (0.11 g, 0.40 mmol, 90%).

5-Amino-6,7-dicyano-3-(4′-tolyl)-3*H*-imidazo[4,5-*b*]pyridine (3a): 91% yield (0.40 mmol); mp 325−326 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.76 (s, 1H), 7.64 (d, J = 5.7 Hz, 2H), 7.38 (d, J = 5.7 Hz, 2H), 7.36 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 158.0, 149.7, 146.5, 138.1, 131.6, 130.0, 128.2, 124.0, 115.2, 114.4, 113.2, 86.0, 20.7; IR (Nujol mull) 2237 (w), 2217 (m), 1635 (s), 1602 (m), 1572 (m), 1522 (m), 1503 (m). Anal. Calcd for $C_{15}H_{10}N_6$: C, 65.68; H, 3.67; N, 30.64. Found: C, 65.60; H, 3.94; N, 30.67.

5-Amino-6,7-dicyano-3-(4′-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine (3b): 93% yield (0.41 mmol); mp 333−334 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.88 (s, 1H), 8.78 (s, 1H), 7.82 (dd, J = 8.7 Hz, J = 5.1 Hz, 2H), 7.45 (t, J = 8.7 Hz, 2H), 7.40 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.4 (d, J = 244 Hz), 158.0, 149.7, 146.5, 130.4 (d, J = 3 Hz), 128.1, 126.5 (d, J = 9 Hz), 116.4 (d, J = 23 Hz), 115.1, 114.4, 113.1, 86.8; IR (Nujol mull) 2242 (w), 2226 (m), 1632 (s), 1601 (m), 1573 (m), 1522 (s), 1504 (m). Anal. Calcd for $C_{14}H_7N_6F$: C, 60.43; H, 2.54; N, 30.20. Found: C, 60.43; H, 2.65; N, 30.13.

5-Amino-6,7-dicyano-3-(4′-methoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine (3c): 90% yield (0.37 mmol); 335−336 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.71 (s, 1H), 7.64 (d, J = 6.1 Hz, 2H), 7.30 (s, 2H), 7.12 (d, J = 6.1 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 159.1, 158.0, 149.9, 146.8, 128.1, 126.8, 125.9, 115.2, 114.6, 114.3, 113.2, 86.6, 55.6; IR (Nujol mull) 2239 (w), 2226 (s), 1651 (s), 1607 (s), 1569 (s), 1524 (s). Anal. Calcd for $C_{15}H_{10}N_6O$: C, 62.07; H, 3.45; N, 28.97. Found: C, 62.52; H, 3.52; N, 28.63.

5-Amino-6,7-dicyano-3-(4′-cyanophenyl)-3*H*-imidazo[4,5-*b*]pyridine (3d): 98% yield (0.41 mmol); mp >355 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.96 (s, 1H) 8.14 (d, J = 6.2 Hz, 2H), 8.09 (d, J = 6.2 Hz, 2H), 7.51 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 158.1, 149.3, 145.7, 138.0, 133.8, 128.4, 123.6, 118.3, 115.0, 114.8, 113.0, 110.3, 87.2; IR (Nujol mull) 2225 (s), 2186 (w), 1634 (s), 1598 (m), 1573 (m), 1518 (s). Anal. Calcd for $C_{15}H_7N_7$: C, 63.16; H, 2.47; N, 34.37. Found: C, 62.92; H, 2.69; N, 33.93.

General Procedure for the Synthesis of 5-Amino-4-(1′-amino-2′,2′-dicyanovinyl)-1-arylimidazoles (4). DBU (0.53 mmol) was added to a solution of malononitrile (0.61−1.21 mmol) in ethanol (10 mL) (for **4b**), in a mixture of ethanol (30 mL) and acetonitrile (5 mL) (for **4a**), or in a mixture of ethanol (3 mL) and DMF (2 mL) (for **4c**), kept in an ice bath. The mixture was stirred in ice for 1 h. A suspension of 5-amino-1-aryl-4-(cyanoformimidoyl)imidazoles **2** (0.44 mmol) in ethanol (2 mL) was added dropwise, and the mixture was stirred in the ice bath for 4 h. The reaction mixture was allowed to stand at −10 °C for 3−4 days, when the solid was filtered and washed with ethanol and diethyl ether.

5-Amino-4-(1′-amino-2′,2′-dicyanovinyl)-1-(4′-tolyl)imidazole (4a): 95% yield (0.42 mmol); mp 223−224 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.74 (s, 2H), 7.52 (s, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 5.67 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.2, 141.8, 138.5, 133.0, 131.3, 130.4, 125.5, 118.1, 43.8, 20.7; IR (Nujol mull) 2207 (s), 2187 (s), 1674 (m), 1622 (s) 1568 (m), 1543 (s), 1519 (m), 1496

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(m). Anal. Calcd for $C_{14}H_{12}N_6 \cdot 0.5H_2O$: C, 61.53; H, 4.79; N, 30.75. Found: C, 61.58; H, 4.94; N, 30.35.

5-Amino-4-(1′-amino-2′,2′-dicyanovinyl)-1-(4′-fluorophenyl)imidazole (4b): 93% yield (0.41 mmol); mp 198−199 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.80 (s, 2H), 7.54 (s, 1H), 7.48−7.53 (m, 2H), 7.42 (t, J = 8.7 Hz, 2H), 5.80 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.9 (d, J = 244 Hz), 163.2, 142.1, 133.0, 130.3 (d, J = 3 Hz), 128.4 (d, J = 10 Hz), 118.1, 116.8 (d, J = 23 Hz), 111.9; IR (Nujol mull) 2204 (s), 2182 (s), 1673 (s), 1629 (m), 1571 (m), 1532 (s), 1518 (s), 1495 (s). Anal. Calcd for $C_{13}H_9N_6F \cdot 0.5H_2O$: C, 56.32; H, 3.61; N, 30.32. Found: C, 56.32; H, 3.27; N, 30.31.

5-Amino-4-(1′-amino-2′,2′-dicyanovinyl)-1-(4′-methoxyphenyl)imidazole (4c): 95% yield (0.39 mmol); mp 243−244 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.71 (s, 2H), 7.49 (s, 1H), 7.36 (d, J = 9.0 Hz, 2H), 7.11 (d, J = 9.0 Hz, 2H), 5.64 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.1, 159.4, 142.1, 133.2, 127.4, 126.4, 118.1, 115.0 114.6, 111.8, 55.5, 43.7. Anal. Calcd for $C_{14}H_{12}N_6O$: C, 60.00; H, 4.29; N, 30.00. Found: C, 59.93; H, 4.46; N, 29.63; IR (Nujol mull) 2220 (s), 2196 (s), 1648 (s), 1620 (s), 1571 (m), 1546 (s), 1517 (s), 1500 (s).

General Procedure for the Synthesis of 5,7-Diamino-3-aryl-6-cyano-3*H*-imidazo[4,5-*b*]pyridines (5). A suspension of 5-amino-4-(1′-amino-2′,2′-dicyanovinyl)-1-arylimidazole **4** (0.30−1.12 mmol) in ethanol (5−10 mL) (for **5a** and **5b**) or DMF (5 mL) (for **5c**) was combined with a catalytic amount of triethylamine (for **5a** and **5b**) or DBU (for **5c**) and the mixture was refluxed for 2 h (for **5a** and **5b**) or 40 h (for **5c**). The solvent was partially removed under vacuum and the white solid was filtered and washed with ethanol and diethyl ether.

5,7-Diamino-6-cyano-3-(4′-tolyl)-3*H*-imidazo[4,5-*b*]pyridine (5a): 40% yield (0.12 mmol); mp 310−312 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.15 (s, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.03 (s, 2H), 6.18 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 159.2, 150.8, 147.6, 138.0, 137.0, 133.0, 129.9, 123.6, 117.3, 116.0, 69.9, 20.8; IR (Nujol mull) 2198 (s), 1664 (s), 1593 (s), 1571 (s), 1519 (s), 1494 (s). Anal. Calcd for $C_{14}H_{12}N_6$: C, 63.62; H, 4.58; N, 31.80. Found: C, 63.64; H, 4.74; N, 31.62.

5,7-Diamino-6-cyano-3-(4′-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine (5b): 80% yield (0.90 mmol); mp 340−341 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.18 (s, 1H), 7.81 (dd, J = 9.0 Hz, J = 4.8 Hz, 2H), 7.38 (t, J = 9.0 Hz, 2H), 7.07 (s, 2H), 6.23 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.8 (d, J = 245 Hz), 159.1, 150.7, 147.5, 137.7, 131.8 (d, J = 3 Hz), 125.6 (d, J = 9 Hz), 117.0, 116.1 (d, J = 23 Hz), 115.9, 69.8; IR (Nujol mull) 2199 (s), 1687 (s), 1611 (s), 1578 (s), 1524 (s), 1512 (s), 1499 (s). Anal. Calcd for $C_{13}H_9N_6F$: C, 58.21; H, 3.38; N, 31.33. Found: C, 58.51; H, 3.55; N, 31.16.

5,7-Diamino-6-cyano-3-(4′-methoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine (5c): 80% yield (0.29 mmol); mp 328−329 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.09 (s, 1H), 7.63 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 7.01 (s, 2H), 6.17 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 159.0, 158.3, 150.6, 147.6, 138.0, 128.3, 125.2, 117.1, 115.8, 114.4, 69.5, 55.5; IR (Nujol mull) 2202 (s), 1686 (s), 1613 (s), 1575 (s) 1499 (m). Anal. Calcd for $C_{14}H_{12}N_6O \cdot 0.25H_2O$: C, 59.05; H, 4.39; N, 29.53. Found: C, 59.47; H, 4.60; N, 29.15.

5,7-Diamino-6-cyano-3-(4′-cyanophenyl)-3*H*-imidazo[4,5-*b*]pyridine (5d). DBU (0.53 mmol) was added to a solution of malononitrile (0.08 g, 1.21 mmol) in ethanol (5 mL) and the mixture was stirred in an ice bath for 1 h. A suspension of 5-amino-4-(cyanoformimidoyl)-1-(4′-cyanophenyl)imidazole **2d** (0.10 g, 0.42 mmol) in ethanol (10 mL) was added dropwise and the mixture was stirred in the ice bath for 4 h. The reaction mixture was allowed to stand at −10 °C for 20 days, when TLC indicated the absence of imidazole **2d**. The solvent was partially removed under reduced pressure, and the white solid was filtered and washed with diethyl ether. The product was identified as the title compound **5d** (0.08 g, 0.29 mmol, 69%). Characterization: mp >350 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.41 (s, 1H), 8.20 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 8.7 Hz, 2H), 7.12 (s, 2H), 6.35 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 159.2, 150.7, 147.2, 139.4, 137.0, 133.6, 122.7, 118.5, 116.8, 116.3, 109.0, 70.0; IR (Nujol mull) 2233 (s), 2194 (s), 1666 (s), 1631 (s), 1603 (s), 1588 (s), 1566 (s), 1521 (s). Anal. Calcd for $C_{14}H_9N_7 \cdot 0.20H_2O$: C, 60.30; H, 3.37; N, 35.18. Found: C, 60.65; H, 3.51; N, 34.92.

Reaction of 5-Amino-4-(cyanoformimidoyl)-1-(4′-tolyl)-imidazole 2a with Malononitrile in the Presence of Triethylamine. Triethylamine (0.06 mmol) was added to a solution of 5-amino-4-(cyanoformimidoyl)-1-(4′-toluyl)imidazole **2a** (0.11 g, 0.47 mmol) and malononitrile (0.04 g, 0.66 mmol) in acetonitrile (5 mL) and the mixture was kept stirring in an ice bath. The mixture was stirred in the ice bath for 6 h and then allowed to stand at −10 °C for 5 days. The solid was filtered and washed with ethanol and diethyl ether, leading to 0.10 g (0.35 mmol, 75%) of the crude mixture (**3a** and **4a** in a 2:1 molar ratio, by ^{1}H NMR).

Reaction of 5-Amino-4-(cyanoformimidoyl)-1-(4′-fluorophenyl)imidazole 2b with Malononitrile in the Presence of Triethylamine. Method A. Triethylamine (0.06 mmol) was added to a solution of 5-amino-4-(cyanoformimidoyl)-1-(4′-fluorophenyl)imidazole **2b** (0.15 g, 0.66 mmol) and malononitrile (0.06 g, 0.91 mmol) in acetonitrile (5 mL) and the mixture was kept stirring in an ice bath. After 5 h, the solid was filtered and washed with ethanol and diethyl ether, leading to 0.13 g (0.47 mmol, 71%) of the crude mixture (3b and 4b in a 2:1 molar ratio, by ^{1}H NMR).

Method B. Triethylamine (0.65 mmol) was added to a solution of malononitrile (0.04 g, 0.61 mmol) in acetonitrile (3 mL) and the mixture was kept stirring in an ice bath. After 10 min, a solution of 5-amino-4-(cyanoformimidoyl)-1-(4′-fluorophenyl)imidazole **2b** (0.10 g, 0.44 mmol) in acetonitrile (3 mL) was added dropwise to the reaction mixture. The mixture was stirred in the ice bath for 5 h and then allowed to stand at −10 °C for 1 day. The yellowish-green precipitate was filtered from a yellow solution and washed with ethanol and diethyl ether, leading to 0.12 g (0.42 mmol, 98%) of the crude mixture (**3b** and **4b** in a 1:3 molar ratio, by ^{1}H NMR).

Method C. Triethylamine (0.65 mmol) was added to a solution of malononitrile (0.07 g, 1.11 mmol) in acetonitrile (3 mL) and the mixture was kept stirring in an ice bath. After 30 min, a solution of 5-amino-4-(cyanoformimidoyl)-1-(4′-fluorophenyl)imidazole **2b** (0.10 g, 0.44 mmol) in acetonitrile (3 mL) was added dropwise to the reaction mixture. The mixture was stirred in the ice bath for 6 h and then allowed to stand at −10 °C for 1 day. The yellowish-green precipitate was filtered from a dark violet solution and washed with ethanol and diethyl ether, leading to 0.08 g (0.29 mmol, 66%) of the crude mixture (**3b** and **4b** in a 1:3 molar ratio, by ^{1}H NMR).

Reaction of 5-Amino-4-(cyanoformimidoyl)-1-(4′-fluorophenyl)imidazole 2b with Ethyl Acetoacetate. Ethyl acetoacetate (0.11 g, 0.85 mmol) was added to a suspension of imidazole **2b** (0.15 g, 0.65 mmol) in acetonitrile (5 mL) and the mixture was kept stirring in an ice bath. The mixture was stirred in the ice bath for 3 h and then at room temperature for 2 days. The orange solid was filtered and washed with diethyl ether to give 6-carbamoyl-2-ethoxyacyl-2-methyl-9-(4-fluorophenyl)-1,2-dihydropurine **10** (0.10 g, 0.28 mmol, 43%). The above experimental procedure was repeated using ethyl acetoacetate (0.26 g, 2.00 mmol) and imidazole **2b** (0.10 g, 0.44 mmol) in acetonitrile (3 mL) and DMF (1 mL). Stirring for 2 days at room temperature led to compound **10** (0.12 g, 0.33 mmol, 76%). When ethyl acetoacetate (0.43 g, 3.30 mmol) and imidazole **2b** (0.10 g, 0.44 mmol) were combined in chloroform (5 mL), compound **10** was also isolated after 2 days at room temperature (0.13 g, 0.36 mmol, 82%). Characterization: mp 212−213 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.20 (s, 1H), 8.13 (s, 2H − amide NH + CH), 9.05 (s, 1H), 7.82 (dd, J = 9.0 Hz, J = 4.8 Hz, 2H), 7.30 (t, J = 9.0 Hz, 2H), 6.70 (s, 1H), 3.97 (dq, J_q = 7.2 Hz, J_d = 1.8 Hz, 2H), 2.77 (d, J = 12.9 Hz, 1H,

C2−CH_AH$_B$), 2.60 (d, J = 12.9 Hz, 1H, C2−CH$_A$$H_B$), 1.55 (s, 3H), 1.07 (t, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 170.0, 162.0, 159.8 (d, J = 241.4 Hz), 156.2, 145.0, 133.1, 132.3 (d, J = 2.5 Hz), 122.9 (d, J = 8.3 Hz), 118.1, 116.0 (d, J = 22.4 Hz), 73.9, 60.1, 45.9, 29.0, 14.1; IR (Nujol mull) 3367 (s), 3330 (s), 3121 (s), 1717 (s), 1693 (s), 1652 (s), 1623 (m) 1582 (s), 1524 (s), 1508 (s). Anal. Calcd for $C_{17}H_{17}N_5O_2F\cdot H_2O$: C, 56.67; H, 5.28; N, 19.44. Found: C, 56.63; H, 5.12; N, 19.32.

Reaction of 5-Amino-4-(cyanoformimidoyl)-1-(4′-fluorophenyl)imidazole 2b with Ethyl Acetoacetate in the Presence of DBU. A solution of ethyl acetoacetate (0.16 g, 1.23 mmol) and DBU (0.53 mmol) in ethanol (5 mL) was stirred in an ice bath for 1 h. A suspension of 5-amino-4-(cyanoformimidoyl)-1-(4′-fluorophenyl)imidazole **2b** (0.10 g, 0.44 mmol) in ethanol (10 mL) was added to the previous solution and the mixture was stirred at 0 °C for 4 h. No reaction occurred (by TLC) and the reaction mixture was stirred at room temperature for 4 days. The solid suspension was filtered, washed with diethyl ether, and identified as imidazole **2b** (0.01 g, 0.04 mmol, 10%). No other products could be isolated from the mother liquor, where imidazole **2b** was identified by TLC as the major product and three other minor components were present.

General Procedure for the Synthesis of 9-Aryl-6-(cyanomethylidene)purine (11). A suspension of imidazole **4** (0.30−0.57 mmol) in triethyl orthoformate (10 mL) was refluxed for 1.5−6 h. The resulting precipitate was filtered and washed with ethanol to give the title compound.

6-(Cyanomethylidene)-9-(4′-methylphenyl)purine (11a): 77% yield (0.44 mmol); mp >355 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.69 (s, 1H), 8.26 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 150.8, 145.7, 145.5, 142.0, 138.3, 131.3, 130.0, 123.9, 123.1, 116.6, 20.7; IR (Nujol mull) 3200 (m), 3062 (m), 2213 (s), 2191 (m), 1627 (s), 1565 (s) 1520 (m). Anal. Calcd for $C_{15}H_{10}N_6$: C, 65.68; H, 3.67; N, 30.64. Found: C, 65.45; H, 4.00; N, 30.50.

6-(Cyanomethylidene)-9-(4′-fluorophenyl)purine (11b): 78% yield (0.29 mmol); mp 281−282 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.00−13.60 (brs, 1H), 8.70 (s, 1H), 8.27 (s, 1H), 7.79 (dd, J = 9.0 Hz, J = 4.7 Hz, 2H), 7.48 (t, J = 9.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.6 (d, J = 244.5 Hz), 150.9, 145.9, 145.6, 142.0, 130.1, 126.5 (d, J = 8.3 Hz), 123.0, 116.5 (d, J = 22.5 Hz); IR (Nujol mull) 3118 (m), 3058 (m), 2204 (s), 2186 (s) 1598 (s), 1542 (m) 1518 (s). Anal. Calcd for $C_{14}H_7N_6F.0.25C_2H_6O$: C, 60.10; H, 2.94; N, 29.02. Found: C, 59.99; H, 2.87; N, 28.99.

General Procedure for the Synthesis of 9-Aryl-6-(cyanomethylidene)-2-methylpurine (12). A suspension of imidazole **4** (0.34−0.37 mmol) in acetic anhydride (10 mL) was refluxed for 1−4 h. The reaction mixture was concentrated in a rotary evaporator and the resulting solid was filtered and washed with ethanol to give the title compound as a cream solid.

6-(Cyanomethylidene)-9-(4′-methylphenyl)-2-methylpurine (12a): 50% yield (0.17 mmol); mp >350 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.60−12.90 (brs, 1H), 8.58 (s, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 2.54 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.8, 150.9, 145.9, 141.6, 138.3, 131.3, 130.0, 124.1, 121.4, 117.0, 116.9, 22.0, 20.7; IR (Nujol mull) 2213 (s), 2194 (s), 1635 (s), 1602 (m), 1518 (m). Anal. Calcd for $C_{16}H_{12}N_6.0.25C_2H_4O_2$: C, 65.35; H, 4.29; N, 27.72. Found: C, 65.53; H, 4.50; N, 27.87.

6-(Cyanomethylidene)-9-(4′-fluorophenyl)-2-methylpurine (12b): 57% yield (0.21 mmol); mp >350 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.60−13.00 (brs, 1H), 8.60 (s, 1H), 7.78 (dd, J = 8.7 Hz, J = 4.8 Hz, 2H), 7.47 (t, J = 8.7 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.6 (d, J = 244.7 Hz), 156.0, 150.9, 145.8, 141.6, 130.1, 126.6 (d, J = 8.8 Hz), 121.4, 117.0, 116.8, 116.5 (d, J = 23.3 Hz), 22.0; IR (Nujol mull) 2237 (m), 2202 (s), 1644 (s), 1600 (m), 1520 (m), 1503 (m). Anal. Calcd for $C_{15}H_9N_6F.0.25C_2H_4O_2$: C, 60.58; H, 3.26; N, 27.36. Found: C, 60.87; H, 3.40; N, 27.16.

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