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The synthesis of imidazo[4,5-*d*]pyridines from a substituted imidazole and acyl or sulfonyl acetonitrile

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Abstract—1-Aryl-5-amino-4-cyanoformimidoyl imidazoles were reacted with acyl and sulfonyl acetonitriles, under mild experimental conditions, leading to imidazo[4,5-*b*]pyridines and imidazo[4,5-*b*]pyridine-5-ones. A reaction intermediate could be isolated in the reaction with methyl cyanoacetate, under carefully controlled experimental conditions. This intermediate cyclized to imidazo[4,5-*b*]pyridine-5-one, in the presence of DBU. Reaction between 5-amino-4-cyanoformimidoyl-1-(4-fluorophenyl)imidazole and acetylacetone, occurred by a different pathway to give a 6-carbamoylpurine.

1. Introduction

Imidazo[4,5-*b*]pyridines are an important class of biologically active compounds showing high affinity to corticotropin-releasing factor[1] and also anticancer,[2] antiviral,[3] antimitotic,[4] and tuberculostatic[5] action depending on the nature and position of substituents on the heterocycle. In addition, certain members of this class display high affinity for the AT_1 receptor, and are thus potent nonpeptide angiotensin II antagonists.[6] Imidazo[4,5-*b*]pyridines were typically prepared by condensation of an appropriate 2,3-diaminopyridine and an electrophilic carbon unit. The reaction of 2-methoxyethylamino-3-aminopyridine with aromatic aldehydes led to 1-methoxyethyl-2-aryl-1*H*-imidazo[4,5-*b*]pyridines.[7] A similar reaction occurred from *N*-substituted nitropyridines, when these compounds were reduced in the presence of aldehydes.[8] 2-Amino-3-nitropyridines have also been used in the regioselective synthesis of either *N*-1 or *N*-3 substituted imidazo[4,5-*b*]pyridines by reaction with aldehydes under carefully selected experimental conditions and in the presence of an appropriate reducing agent.[9] Imidazo[4,5-*b*]pyridine-5-ones are difficult to prepare by this method and only a few synthetic approaches have been reported in the literature. Reaction of 5-amino-1,2-disubstituted imidazole with dialkyl acetylenedicarboxylate, at room temperature, led to a dialkyl 1-(5-amino-1,2-disubstituted imidazol-4-yl)ethylene-1,2-dicarboxylate in yields ranging from 35 to 44%. One of these compounds, dimethyl 1-(5-amino-1,2-dimethylimidazol-4-yl)ethylene-1,2-dicarboxylate, underwent thermal cyclization when heated at 190 °C (1 min) giving methyl 2,3-dimethyl-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate in 36% yield.[10] Oxidation of 3-(2-(4-benzylphenoxy)ethyl)-3*H*-imidazo[4,5-*b*]pyridine with *m*-CPBA provided the *N*-oxide formation in the pyridine ring. Treatment of this compound with trifluoroacetic anhydride yielded the corresponding 3-substituted 3*H*-imidazo[4,5-*b*]pyridine-5(4*H*)-one. The parent imidazo[4,5-*b*]pyridine proved to be a potent inhibitor of leukotriene A4 hydrolase, and the functionalization to the imidazo[4,5-*b*]pyridine-5(4*H*)one considerably improved the enzyme inhibitory potency, as well as a good oral activity in a mouse in vivo assay.[11]

2. Results and discussion

In our research group, we have been studying the reactivity of 5-amino-4-cyanoformimidoyl imidazoles **1**, as versatile precursors to 6-substituted purines[12] and other fused nitrogen heterocycles.[13] The cyanoformimidoyl unit plays a fundamental role in the reactivity of these compounds.

In this work, functionalized imidazo[4,5-*b*]pyridines **5** were isolated in good yield from the reaction between *N*-aryl-5-amino-4-(cyanoformimidoyl)-imidazoles **1** and 3-phenyl-3-oxopropanenitrile **2a** or 3-(7-methyl-1*H*-indol-3-yl)-3-oxopropanenitrile **2b**, in ethanol/acetonitrile or ethanol/DMF. Product **5** gradually precipitated from the homogeneous solution as a white solid and was isolated by filtration (Scheme 1). The reaction must proceed through the formation of intermediate **4**, generated from adduct **3** by elimination of ammonia. Nucleophilic attack of the amino group in the 5-position to the acyl substituent was the only observed pathway, leading to the imidazo[4,5-*b*]pyridine **5**. Attempts to isolate this intermediate from

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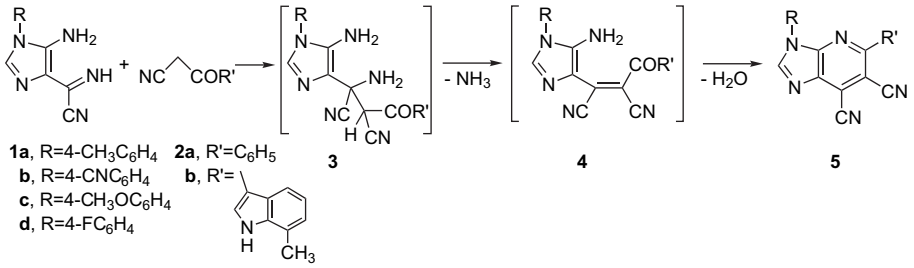


1a, R=4-$CH_3C_6H_4$ **2a**, R'=C_6H_5 **3** **4** **5**
b, R=4-CNC_6H_4 **b**, R'=
c, R=4-$CH_3OC_6H_4$
d, R=4-FC_6H_4

Compound	R	R´	Reaction Conditions[a)]	Yield (%)
5a	4-MeC_6H_4	C_6H_5	ethanol:acetonitrile (5:1), 4h	94
5b	4-CNC_6H_4	C_6H_5	ethanol:DMF(10:3), 8 days	70
5c	4-$MeOC_6H_4$	C_6H_5	ethanol:DMF (2:1), 20 h	79
5d	4-FC_6H_4	C_6H_5	ethanol:acetonitrile (5:1), 4 h	87
			acetonitrile:diethyl ether (3:20), 4 h (0 °C); 1 day	61
5e	4-CNC_6H_4	Indolyl	ethanol:DMF (10:3), 7 days	63
5f	4-$MeOC_6H_4$	Indolyl	Ethanol:DMF (2:1), 72 h	78
5g	4-FC_6H_4	Indolyl	ethanol:acetonitrile (10:3), 30 min	81

[a)] All the experiments were carried out at room temperature

Scheme 1.

imidazole **1d** and 3-phenyl-3-oxopropanenitrile in acetonitrile and diethyl ether (3:20) failed, as the only product isolated was again the imidazo[4,5-*b*]pyridine **5d** (61%).

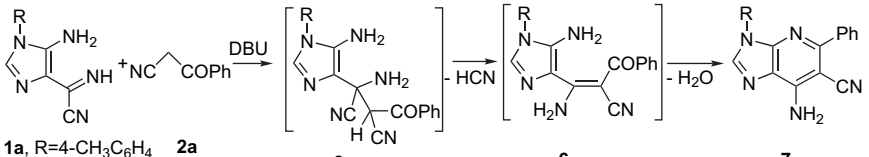
When imidazoles **1a** and **1d** were reacted with 3-phenyl-3-oxopropanenitrile in the presence of one molar equivalent of DBU, elimination of HCN from adduct **3a** was the major pathway, leading to the 7-amino-imidazo[4,5-*b*]pyridines **7** in very good yield (Scheme 2). Imidazole **6** must be the precursor of **7**, which was formed by intramolecular cyclization between the amino and carbonyl groups. Structures analogous to **5** and **7** were previously isolated when imidazole **1** was reacted with malononitrile in the absence and in the presence of DBU, respectively.[13b]

Imidazoles **1a**, **1c**, and **1d** were also reacted with phenylsulfonyl acetonitrile **2c** in ethanol/acetonitrile or ethanol/acetonitrile/DMF (Scheme 3). When the homogeneous solution was stirred at room temperature, the product gradually precipitated as a white solid. The compound was identified as having structure **8** on the basis of spectroscopic analysis.

The reaction of imidazole **1a** with phenylsulfonyl acetonitrile in the presence of 1 equiv of DBU led to a complex mixture after 7 days at room temperature and no attempts were made to identify their components.

The reaction of imidazoles **1a**–**d** with methyl cyanoacetate **2d** using acetonitrile or acetonitrile/DMF as solvent (Scheme 4) led to the formation of imidazo[4,5-*b*]pyridine-5-ones **11**, as was previously communicated.[14] The product precipitated as the ammonium salt **10** and was isolated by filtration.

Addition of acetic acid to a solution of compounds **10a**–**c** in water/ethanol enabled the isolation of the corresponding imidazo[4,5-*b*]pyridine-5-ones **11** in excellent yield. Compound **10d** could not be fully neutralized by acetic acid

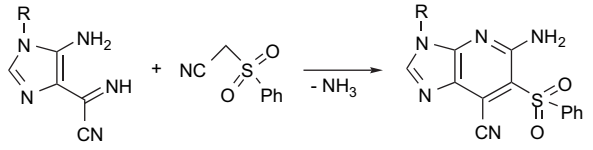


1a, R=4-$CH_3C_6H_4$ **2a** **3** **6** **7**
d, R=4-FC_6H_4

Compound	R	Reaction Conditions[a)]	Yield (%)
7a	4-MeC_6H_4	DBU (1.2 eq.); **2a** (1.2 eq.) ethanol:acetonitrile (5:8); 4h (0 °C); 5 days	61
		DBU (1.2 eq.); **2a** (1.2 eq.) ethanol:acetonitrile (1:1); 4h (0 °C); 10 days	96
7d	4-FC_6H_4	DBU (1.2 eq.); **2a** (1.2 eq.) ethanol:acetonitrile (5:8); 4h (0 °C); 5 days	71

[a)] All the experiments were carried out at room temperature

Scheme 2.



1a, R=4-$CH_3C_6H_4$
c, R=4-$CH_3OC_6H_4$
d, R=4-FC_6H_4

2c

8

Compound	R	Reaction Conditions[a)]	Yield (%)
8a	4-MeC_6H_4	ethanol:acetonitrile (5:1), 3 days	88
8c	4-$MeOC_6H_4$	ethanol:DMF:acetonitrile(10:5:2), 5 days	72
8d	4-FC_6H_4	ethanol:acetonitrile (2:1), 5 days	82

[a)] All the experiments were carried out at room temperature

Scheme 3.

(pK_a=4.76),[15] as the product consistently incorporated half an equivalent of ammonia, according to elemental analysis and ^{1}H NMR data. Neutralization of **10d** was achieved when trifluoroacetic acid (pK_a=0.23)[15] was added to a solution of the compound in a mixture of aqueous ethanol and DMF.

The reaction pathway must occur by initial formation of intermediate **9**, which could be isolated from reaction of **1d** with methyl cyanoacetate in acetonitrile/diethyl ether (1:10), at −10 °C. The orange solid **9d** cyclized to compound **10d** after refluxing for 1 h in ethanol solution, in the presence of DBU. Compound **9d** showed a very intense carbonyl absorption in the IR spectrum (1707 cm^{-1}) and the stretching vibration of the two cyano groups corresponded to two intense bands at 2219 and 2202 cm^{-1}. In the ^{13}C NMR spectrum, these signals were identified at δ 116.5 and 115.3 ppm. The ester carbonyl group is at δ 163.0 ppm and the C–H signal, at δ 137.0 ppm, is typical of an imidazole structure. This was confirmed by ^{1}H NMR spectrum, where the signal for this proton is at δ 7.77 ppm.

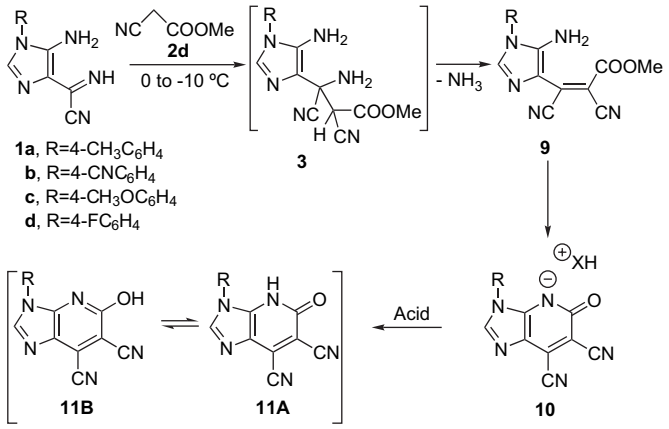
For the ammonium salts **10**, the IR spectrum confirmed the presence of two cyano groups showing a strong band at around 2210 cm^{-1} and a medium/weak signal in the 2230–2239 cm^{-1} region. In the ^{13}C NMR spectrum, these groups were present at around δ 118.5 and 114.5 ppm. The lactam carbonyl was in the δ 166.9–168.1 ppm region and the C–H signal was at δ 141.6–143.7 ppm region. In the ^{1}H NMR spectrum this proton appears in the δ 8.39–8.65 ppm region, and a singlet at around δ 7.2 ppm integrating for four protons was assigned to the ammonium ion.

For compounds **5**, **7**, and **11**, the IR spectra showed a single intense band in the 2206–2243 cm^{-1} region, assigned to the stretching vibration of the cyano group. A minor shoulder was also present in the spectrum of compounds **5a**, **5c**, and **5d**, for the second cyano substituent. For compounds **8**, a weak absorption band was present in the 2230–2236 cm^{-1} region. The carbonyl stretching vibration is absent in the spectrum of compounds **11a–c**, which shows an intense band in the 1590–1600 cm^{-1} region. This may be an indication that **11B** is the predominant tautomer in the solid state. Compound **11d** showed an intense band at 1650 cm^{-1}, confirming the presence of a six-membered lactam ring. In the ^{13}C NMR spectrum it was possible to identify the signals for the cyano groups at δ 112–113 and 116–117 ppm (for compounds **5**), at δ 117.4 ppm (for compounds **7**), and in the δ 111–114 ppm region for compounds **8** and **11** The C–H signal in the δ 141.5–151 ppm region confirms the presence of the imidazo-pyridine system in these compounds. The signal for the lactam carbonyl in compounds **11a–d** is also consistently present at around δ 162.5 ppm. In the ^{1}H NMR spectrum of these compounds a very acidic N–H was identified as a broad singlet in the δ 13–14 ppm. For compounds **5**, **7**, **8**, and **11**, the C–H signal between δ 8.6 and 9.5 ppm confirms that a fused aromatic system is present.

DBU (2 equiv) was added to a solution of imidazole **1d** and methyl cyanoacetate in acetonitrile/diethyl ether, conditions that would favor elimination of HCN from **3d** to give an intermediate analogous to **6**, ultimately leading to the 7-amino-6-cyanoimidazo[4,5-*b*]pyridine-5-one structure. The major product was 5-amino-1-aryl-4-cyanoimidazole, together with traces of imidazole **1d** indicating that, in the presence of base, elimination of HCN from imidazole **1d** is much faster than reaction with methyl cyanoacetate.

In the reaction of imidazole **1** with phenylsulfonyl acetonitrile and methyl cyanoacetate, elimination of ammonia from intermediate **3** was the only observed pathway. The behavior of 3-phenyl-3-oxoacetonitrile compared with that of malononitrile,[13b] leading to imidazo[4,5-*b*]pyridine **5** or **7** depends on the presence or absence of DBU in the reaction mixture. The pathway leading to **7** (by elimination of HCN from adduct **3**) seems to occur only if the carbon acid has a pK_a lower than ca. 12 (values obtained in DMSO solution). This is the case of 3-oxo-3-phenylacetonitrile (pK_a=10.2)[15] and malononitrile (pK_a=11.1).[16] Phenylsulfonyl acetonitrile (pK_a=12.0)[15] or methylcyanoacetate (pK_a=13.1)[17] are weaker carbon acids and the formation of the carbanion from the active methylene compound does not occur in an appreciable extent by the addition of DBU (pK_a ca. 12)[18] to the active methylene compound (Scheme 5).

The formation of the anion from the carbon acid would generate the intermediate **3A** that easily eliminates the cyanide



Compound	R	Reaction Conditions	Yield (%)
9d	4-FC_6H_4	acetonitrile:diethyl ether (1:10) 4 h (0 ºC); 1 day (-10 ºC)	36[a]
10a X=NH_3	4-MeC_6H_4	acetonitrile:DMF (3:2) 6 h (0 ºC); 1 day (-10 ºC)	88[a]
10b X=NH_3	4-CNC_6H_4	acetonitrile:DMF (5:2) 6 h (0 ºC); 8 days (-10 ºC)	86[a]
10c X=NH_3	4-$MeOC_6H_4$	acetonitrile:DMF (1:1) 6 h (0 ºC); 3 days (-10 ºC)	86[a]
10d X=NH_3	4-FC_6H_4	acetonitrile:DMF (1:1) 8 h (0 ºC); 15 h (-10 ºC)	86[a]
10d X=DBU	4-FC_6H_4	Ethanol; DBU 1 h (reflux)	82[b]
11a	4-MeC_6H_4	H_2O:Ethanol:HOAc (5:2:1.5) 30 min (rt)	84[c]
11b	4-CNC_6H_4	H_2O:Ethanol:HOAc (5:2:1.5) 30 min (rt)	79[c]
11c	4-$MeOC_6H_4$	H_2O:Ethanol:HOAc (5:3:1) 30 min (rt)	82[c]
11d	4-FC_6H_4	H_2O:Ethanol:DMF:CF_3CO_2H (5:3:2:0.04), 30 min (rt)	50[c]

[a] Yield and reaction conditions from imidazole **1** and methyl cyanoacetate.
[b] Yield and reaction conditions from imidazole **9d.**
[c] Yield and reaction conditions from the ammonium salt of imidazo[4,5-*b*]pyridine-5-one **10.**

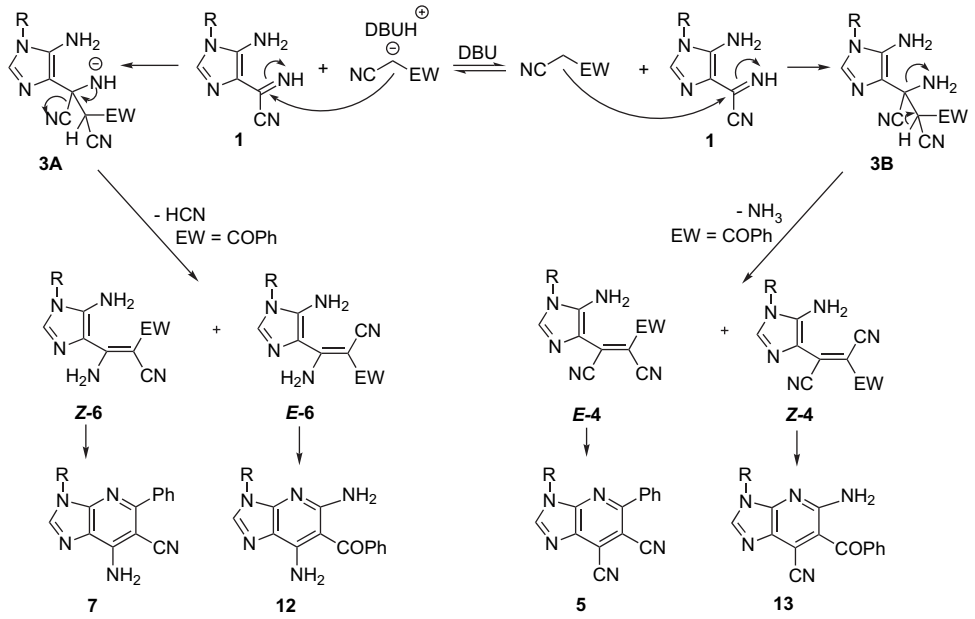
Scheme 4.

ion, leading to imidazole **6** in either the *Z* or the *E* configuration. The carbon acid can also react with the cyanoformimidoyl substituent of imidazole **12**, but in this case the proton would be intramolecularly transferred to the imine nitrogen, to generate the amine. The acidic proton can further protonate this amine unit, leading to the formation of imidazoles **4**, also in either the *Z* or the *E* configuration, upon elimination of ammonia.

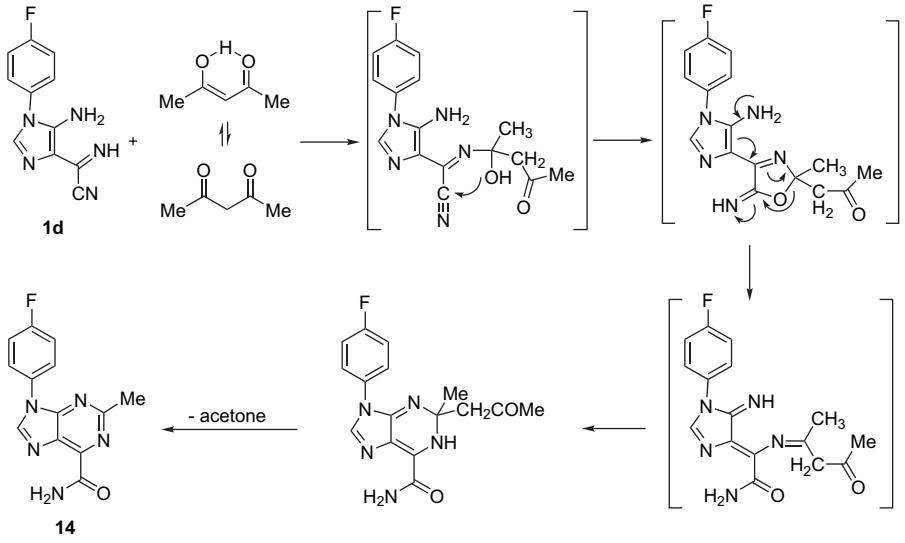
The formation of imidazo[4,5-*b*]pyridines **5** and **13** or **7** and **12** was expected by intramolecular cyclization of intermediate **4** or **6**, respectively. In the present work, compounds **5** and **7** were the only products isolated, possibly because these reactions occur with elimination of 1 equiv of water, and are thus energetically favored.

The presence of only one carbonyl/sulfoxide group in the active methylene compound also determines this reaction pathway. The reaction between **1d** and acetylacetone, which has a pK_a value of 13.3[19] (similar to that of methylcyanoacetate), under similar conditions to those used above, gave the 6-carbamoyl purine **14**, formed by the pathway shown in Scheme 6. The formation of 6-carbamoyl purines is known to occur when 5-amino-4-cyanoformimidoyl imidazoles **1** react with aldehydes or ketones[12a–c,13] and was also reported in the presence of ethyl acetoacetate.[13b]

In conclusion, a mild and efficient synthesis of biologically interesting functionalized imidazo[4,5-*b*]pyridines and imidazo[4,5-*b*]pyridine-5-ones has been developed. A limited number of methods were previously reported for the



Scheme 5.



Scheme 6.

preparation of these structures, which may be biologically important. The compounds prepared have been submitted to TAACF[20] for screening their tuberculostatic activity and studies on their antioxidant properties are also in progress.

3. Experimental

3.1. General techniques

The 5-amino-1-aryl-4-(cyanoformimidoyl)imidazoles **1a**–**d** used in this work were prepared according to previously described procedures.[21] Compound **2b** was prepared according to the procedure described by Bergman et al.[22] NMR spectra were recorded on a Varian Unity Plus 300 spectrometer with TMS as an internal standard. The fluorine coupling constants in the ^{13}C NMR spectra were verified in all the samples, and confirmed using the HMBC and HMQC techniques (to identify the signals for the aromatic Ci and Cp). The IR spectra were obtained with an FTIR Bomem-MB104 spectrophotometer using Nujol mulls and NaCl plates. Elemental analysis was performed on an LECO CHNS-932 instrument. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

3.2. General procedure for the synthesis of 3-aryl-5-phenyl-3*H*-imidazo[4,5-*b*]pyridine-6,7-dicarbonitriles (5a–d) and 3-aryl-5-(7-methyl-1*H*-indol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-6,7-dicarbonitriles (5e–g)

A solution of 5-amino-1-aryl-4-cyanoformimidoyl imidazole (0.65–1.33 mmol) in ethanol/DMF (for **5b**, **5c**, **5e**, and **5f**), ethanol/acetonitrile (for **5a**, **5d**, and **5g**) (3–5 mL),

or acetonitrile/diethyl ether (3:20) (for **5d**) was combined with 3-oxo-3-phenylpropanenitrile or (7-methyl-1*H*-indol-3-yl)-3-oxopropanenitrile (1.5 molar equiv) and the solution was stirred at room temperature or in an ice bath. The product **5** gradually precipitates from solution as a white solid and is filtered after 30 min to 8 days.

3.2.1. 3-(4′-Tolyl)-5-phenyl-3*H*-imidazo[4,5-*b*]pyridine-6,7-dicarbonitrile (5a). Yield 0.28 g, 0.83 mmol (94%); mp 278–279 °C. IR (Nujol mull) 2224 (m), 2237 (w), 1593 (s), 1560 (w), 1526 (w), 1517 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=2.39 (s, 3H, CH_3), 7.44 (d, J=8.4 Hz, 2H), 7.58–7.60 (m, 3H), 7.78 (d, J=8.4 Hz, 2H), 7.85–7.89 (m, 2H), 9.36 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=20.7, 103.5, 113.0, 114.5, 116.2, 123.9, 128.7, 129.3, 130.2, 130.4, 131.2, 136.6, 137.4, 138.5, 148.7, 151.0, 156.5. Anal. Calcd for $C_{21}H_{13}N_5$ (335.37): C, 75.21; H, 3.91; N, 20.88. Found: C, 75.14; H, 3.98; N, 20.90.

3.2.2. 3-(4′-Cyanophenyl)-5-phenyl-3*H*-imidazo[4,5-*b*]pyridine-6,7-dicarbonitrile (5b). Yield 0.16 g, 0.44 mmol (70%); mp 301–302 °C. IR (Nujol mull) 2229 (s), 1597 (s), 1578 (w), 1510 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=7.60–7.62 (m, 3H), 7.89–7.92 (m, 2H), 8.16 (d, J=8.7 Hz, 2H), 8.25 (d, J=8.7 Hz, 2H), 9.51 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=104.0, 111.0, 112.8, 114.8, 115.9, 118.1, 128.7, 129.1, 129.3, 130.5, 133.5, 134.8, 136.4, 137.5, 148.4, 150.5, 156.7. Anal. Calcd for $C_{21}H_{10}N_6\cdot 0.2$DMF (360.97): C, 71.87; H, 3.18; N, 24.06. Found: C, 71.74; H, 3.40; N, 23.72.

3.2.3. 3-(4′-Methoxyphenyl)-5-phenyl-3*H*-imidazo[4,5-*b*]pyridine-6,7-dicarbonitrile (5c). Yield 0.29 g, 0.83 mmol (79%); mp 238–239 °C. IR (Nujol mull) 2243 (w), 2255 (m), 1612 (w), 1598 (s), 1520 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=3.83 (s, 3H, OCH_3), 7.16–7.19 (d, 2H, J=9.0 Hz), 7.57–7.60 (d, 2H, J=9.0 Hz), 7.56–7.60 (m, 3H), 7.84–7.90 (m, 2H), 9.31 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=55.6, 103.4, 113.0, 114.4, 114.8, 116.1, 125.6, 126.4, 128.7, 129.3, 130.3, 134.3, 136.6, 148.8, 151.1, 156.4, 159.3. Anal. Calcd for $C_{21}H_{13}N_5O$ (351.37): C, 71.80; H, 3.73; N, 19.93. Found: C, 71.74; H, 3.81; N, 19.91.

3.2.4. 3-(4′-Fluorophenyl)-5-phenyl-3*H*-imidazo[4,5-*b*]pyridine-6,7-dicarbonitrile (5d). Yield 0.13 g, 0.38 mmol (87%); mp 276–278 °C. IR (Nujol mull) 2226 (m), 2237 (w), 1606 (w), 1593 (s), 1565 (s), 1517 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=7.50 (t, J=8.7 Hz, 2H), 7.57–7.59 (m, 3H), 7.82–7.89 (m, 2H), 7.97 (dd, J=8.7, 4.7 Hz, 2H), 9.36 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=103.6, 112.9, 114.5, 116.1, 116.7 (J=23.2 Hz), 126.4 (J=8.9 Hz), 128.7, 129.3, 130.0 (J=3.2 Hz), 130.4, 134.4, 136.5, 148.7, 151.0, 156.6, 161.7 (J=244.9 Hz). Anal. Calcd for $C_{20}H_{10}N_5F$ (339.33): C, 70.79; H, 2.97; N, 20.64. Found: C, 70.42; H, 3.12; N, 20.65.

3.2.5. 3-(4′-Cyanophenyl)-5-(7-methyl-1*H*-indol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-6,7-dicarbonitrile (5e). Yield 0.16 g, 0.40 mmol (63%); mp above 350 °C. IR (Nujol mull) 2233 (m), 1594 (s), 1530 (s), 1514 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=2.48 (s, 3H, CH_3), 7.03 (m, 2H), 7.97 (t, 1H), 8.31 (s, 1H), 8.15 (d, J=8.4 Hz, 2H), 8.24 (d, J=8.4 Hz, 2H), 9.34 (s, 1H), 11.8 (br, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ=16.7, 100.5, 110.8, 112.2, 115.0, 117.1, 118.2, 121.3, 121.4, 123.3, 123.9, 125.0, 128.5, 132.4, 133.8, 135.7, 137.7, 148.4, 148.9, 152.7. Anal. Calcd for $C_{24}H_{13}N_7\cdot 0.2H_2O$ (403.02): C, 71.53; H, 3.35; N, 24.33. Found: C, 71.29; H, 3.63; N, 24.09.

3.2.6. 3-(4′-Methoxyphenyl)-5-(7-methyl-1*H*-indol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-6,7-dicarbonitrile (5f). Yield 0.27 g, 0.65 mmol (78%); mp above 350 °C. IR (Nujol mull) 2221 (m), 1656 (m), 1616 (w), 1600 (m), 1561 (w), 1532 (s), 1517 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=2.48 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.97 (d, J=4.8 Hz, 2H), 7.18 (d, J=8.7 Hz, 2H), 7.81 (d, J=8.7 Hz, 2H), 8.01 (m, 1H), 8.30 (s, 1H), 9.13 (s, 1H), 11.85 (br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ=16.7, 55.6, 100.0, 112.4, 113.1, 114.6, 117.4, 119.0, 121.1, 121.2, 123.2, 125.2, 125.6, 126.7, 128.2, 132.1, 135.7, 148.8, 149.7, 152.6, 159.2. Anal. Calcd for $C_{24}H_{16}N_6O\cdot 0.75H_2O$ (417.94): C, 68.97; H, 4.22; N, 20.11. Found: C, 69.18; H, 4.613; N, 20.49.

3.2.7. 3-(4′-Fluorophenyl)-5-(7-methyl-1*H*-indol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-6,7-dicarbonitrile (5g). Yield 0.29 g, 0.71 mmol (81%); mp 334–336 °C. IR (Nujol mull) 2228 (m), 1599 (m), 1536 (m), 1518 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=2.48 (s, 3H, CH_3), 6.98–7.03 (m, 2H), 7.54 (t, J=8.7 Hz, 2H), 7.96–8.01 (m, 3H), 8.33 (s, 1H), 9.22 (s, 1H), 11.90 (s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ=16.7, 100.4, 112.4, 113.1, 114.9, 116.5 (J=22.9 Hz), 117.3, 118.9, 121.2, 121.4, 123.2, 125.3, 126.6 (J=8.9 Hz), 128.4, 130.2 (J=2.9 Hz), 132.2, 135.8, 149.0, 149.7, 152.8, 161.7 (J=244.6 Hz). Anal. Calcd for $C_{23}H_{13}N_6F\cdot 1.75H_2O$ (423.93): C, 65.17; H, 3.92; N, 19.82. Found: C, 65.08; H, 4.27; N, 19.47.

3.3. General procedure for the reaction of 5-amino-1-aryl-4-cyanoformimidoylimidazole with 3-oxo-3-phenylpropanenitrile in the presence of DBU

3-Oxo-3-phenylpropanenitrile (0.8 mmol) was added to a solution of DBU (0.8 mmol) in ethanol (5 mL) and the mixture was stirred in an ice bath for 1 h. A solution of imidazole **1** (0.67 mmol) in acetonitrile (8 mL) was added to the reaction mixture, which was stirred in an ice bath for 4 h, and then at room temperature for 5–10 days. The suspension was filtered and washed with diethyl ether, leading to a white solid identified as compound **7**.

3.3.1. 7-Amino-3-(4-tolylphenyl)-5-phenyl-3*H*-imidazo[4,5-*b*]pyridine-6-carbonitrile (7a). Yield 0.19 g, 0.53 mmol (61%); mp 226–227 °C. IR (Nujol mull) 2207 (s), 1650 (s), 1604 (s), 1562 (m) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=2.36 (s, 3H, CH_3), 7.37 (d, J=8.4 Hz, 2H), 7.49 (s, 2H, NH_2), 7.45–7.50 (m, 3H), 7.74 (d, J=8.4 Hz, 2H), 7.75–7.72 (m, 2H), 8.62 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=20.6, 84.6, 121.0, 123.4, 128.1, 128.9, 129.2, 129.9, 132.5, 137.2, 138.9, 141.5, 146.7, 150.5, 158.1. Anal. Calcd for $C_{20}H_{15}N_5\cdot 1.7H_2O$ (356.01): C, 67.48; H, 5.19; N, 19.67. Found: C, 67.49; H, 5.08; N, 19.64.

3.3.2. 7-Amino-3-(4-fluorophenyl)-5-phenyl-3*H*-imidazo[4,5-*b*]pyridine-6-carbonitrile 7d. Yield 0.17 g, 0.48 mmol (71%); mp 209–210 °C. IR (Nujol mull) 2206 (s), 1662 (s), 1604 (m), 1565 (m) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=7.43 (t, J=9.0 Hz, 2H), 7.46–7.51 (m, 3H), 7.71–7.75 (m, 2H), 7.94 (dd, J=9.0, 5.0 Hz, 2H), 8.65 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=84.8, 116.3 (d, J=23.0 Hz), 120.9, 125.8 (d, J=8.6 Hz), 128.2, 128.9, 129.2, 131.3 (d, J=2.9 Hz), 138.8, 141.5, 146.7, 150.5, 158.3, 161.0 (d, J=243.0 Hz). Anal. Calcd for $C_{19}H_{12}N_5F\cdot 1.5H_2O$ (356.36): C, 64.04; H, 4.24; N, 19.65. Found: C, 63.83; H, 4.195; N, 19.40.

3.4. General procedure for the synthesis of 5-amino-3-aryl-6-(phenylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carbonitriles (8a–d)

A solution of 5-amino-1-aryl-4-cyanoformimidoyl imidazole **1** (0.62–0.87 mmol) in ethanol/acetonitrile (3–5 mL) (for **8a** and **8d**) or ethanol/acetonitrile/DMF (for **9c**) was combined with phenylsulfonyl acetonitrile (1.5–1.6 molar equivalent) and the homogeneous solution was stirred at room temperature. The product gradually precipitates from solution as a white solid and is filtered after 3–5 days.

3.4.1. 5-Amino-3-(4′-tolyl)-6-(phenylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carbonitrile (8a). Yield 0.23 g, 0.59 mmol (88%); mp 268–269 °C. IR (Nujol mull) 2231 (w), 1802 (w), 1607 (s), 1583 (s), 1573 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=2.35 (s, 3H, CH_3), 7.33 (d, J=8.4 Hz, 2H), 7.34 (s, 2H, NH_2), 7.62 (t, J=8.4 Hz, 2H), 7.67–7.75 (m, 3H), 8.07–8.10 (d, 2H, J=8.7 Hz), 8.76 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=20.6, 111.2, 111.6, 112.7, 123.9, 126.6, 129.8, 129.8, 131.3, 131.5, 134.5, 137.9, 140.4, 147.0, 149.9, 154.5. Anal. Calcd for $C_{20}H_{15}N_5O_2S$ (389.42): C, 61.69; H, 3.88; N, 17.98. Found: C, 61.47; H, 3.90; N, 17.97.

3.4.2. 5-Amino-3-(4′-methoxyphenyl)-6-(phenylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carbonitrile (8c). Yield 0.18 g, 0.44 mmol (72%); mp 248–249 °C. IR (Nujol mull) 2229 (w), 1802 (w), 1603 (s), 1582 (s), 1572 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=3.09 (s, 3H, OCH_3), 7.09 (d, J=9.0 Hz, 2H), 7.33 (s, 2H, NH_2), 7.63 (d, J=9.0 Hz, 2H), 7.67 (t, J=7.8 Hz, 2H), 7.76 (t, J=7.8 Hz, 1H), 8.08 (d, J=7.8 Hz, 2H), 8.70 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=55.6, 111.1, 111.6, 112.7, 114.6, 125.9, 126.6, 126.8, 129.8, 131.1, 134.5, 140.4, 147.3, 150.1, 154.5, 159.1. Anal. Calcd for $C_{20}H_{15}N_5O_3S$ (405.42): C, 59.25; H, 3.73; N, 17.27; S, 7.90. Found: C, 59.15; H, 4.03; N, 17.20; S, 7.97.

3.4.3. 5-Amino-3-(4′-fluorophenyl)-6-(methylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carbonitriles (8d). Yield 0.28 g, 0.71 mmol (82%); mp 279–280 °C. IR (Nujol mull) 2236 (w), 1743 (w), 1616 (s), 1598 (s), 1573 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=7.38 (s, 2H, NH_2), 7.42 (t, J=9.0 Hz, 2H), 7.67 (t, J=7.5 Hz, 2H), 7.76 (t, J=7.5 Hz, 1H), 7.81 (dd, J=4.8, 9.0 Hz), 8.09 (d, 2H, J=7.5 Hz), 8.77 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=111.3, 111.7, 112.6, 116.3 (J=22.9 Hz), 126.5 (J=8.9 Hz), 126.6, 129.8, 130.4 (J=2.9 Hz), 131.1, 134.5, 140.4, 147.0, 150.0, 154.6, 161.4 (J=244.3 Hz). Anal. Calcd for $C_{19}H_{12}N_5O_2FS$ (393.38): C, 58.01; H, 3.07; N, 17.80; S, 8.15. Found: C, 58.19; H, 3.39; N, 17.75; S, 8.18.

3.5. Reaction of 5-amino-4-cyanoformimidoyl-1-(4′-tolylphenyl)imidazole with phenylsulfonyl acetonitrile in the presence of DBU

A solution of 5-amino-4-cyanoformimidoyl-1-(4′-tolylphenyl)imidazole **1a** (0.20 g, 0.89 mmol) in acetonitrile (3 mL) was added to a solution of phenylsulfonyl acetonitrile (0.30 g, 1.80 mmol) and DBU (0.28 g, 1.80 mmol) in ethanol (10 mL) that had been stirred in an ice bath for 2 h. The solution was stirred in the ice bath for another 3 h and the mixture was kept standing at −10 °C for 3 days. The reaction was followed by TLC, which showed that a complex mixture had been formed, together with extensive degradation.

3.6. General procedure for the synthesis of the ammonium salt of 3-aryl-6,7-dicyano-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (10a–d)

A solution of 5-amino-1-aryl-4-cyanoformimidoyl imidazole **1** (0.4–1.2 mmol) in acetonitrile (3–5 mL) and dimethylformamide (1–3 mL) was combined with methyl cyanoacetate (1.4–2.4 molar equivalent) and the mixture was stirred in an ice bath for 6–8 h. After standing at −10 °C for 1–8 days, the solid suspension was filtered and washed with diethyl ether. A second crop of the same product could be recovered from the mother liquor after concentration on the rotary evaporator.

3.6.1. Ammonium salt of 6,7-dicyano-3-(4′-tolyl)-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (10a). Yield 0.025 g, 0.78 mmol (88%); mp 317–318 °C. IR (Nujol mull) 2239 (w), 2211 (m), 1598 (m), 1585 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=2.35 (s, 3H), 7.20 (s, 4H), 7.32 (d, J=8.4 Hz, 2H), 7.69 (d, J=8.4 Hz, 2H), 8.42 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=20.6, 92.7, 113.5, 114.1, 118.9, 122.6, 123.5, 129.6, 132.7, 136.3, 142.3, 151.2, 168.1. Anal. Calcd for $C_{15}H_9N_5O\cdot NH_3\cdot 1.5H_2O$ (319.32): C, 56.42; H, 4.74; N, 26.32. Found: C, 56.56; H, 4.61; N, 26.08.

3.6.2. Ammonium salt of 6,7-dicyano-3-(4′-cyanophenyl)-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (10b). Yield 0.13 g, 0.42 mmol (86%); mp 345–346 °C. IR (Nujol mull) 2235 (w), 2211 (s), 1652 (s), 1598 (s), 1587 (s), 1553 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=7.20 (s, 4H), 8.00 (d, J=9.0 Hz, 2H), 8.21 (d, J=9.0 Hz, 2H), 8.65 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=93.20, 108.8, 113.9, 114.0, 118.6, 118.5, 122.2, 123.7, 133.5, 139.0, 141.6, 150.9, 168.0. Anal. Calcd for $C_{15}H_6N_6O\cdot NH_3\cdot 0.2H_2O$ (306.89): C, 58.71; H, 3.08; N, 31.95. Found: C, 58.85; H, 3.15; N, 31.78.

3.6.3. Ammonium salt of 6,7-dicyano-3-(4′-methoxyphenyl)-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (10c). Yield 0.11 g, 0.35 mmol (86%); mp 306–307 °C. IR (Nujol mull) 2235 (w), 2211 (s), 1652 (s), 1598 (s), 1587 (s), 1553 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=3.80 (s, 3H), 7.07 (d, J=9.0 Hz, 2H), 7.21 (br s, 4H),

7.67 (d, J=9.0 Hz, 2H), 8.39 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=55.5, 92.6, 113.5, 114.2, 114.4, 118.9, 124.6, 128.0, 142.8, 158.2, 168.0. Anal. Calcd for $C_{15}H_9N_5O_2\cdot NH_3\cdot 0.2H_2O$ (311.90): C, 57.76; H, 4.01; N, 26.95. Found: C, 57.69; H, 4.22; N, 26.61.

3.6.4. Ammonium salt of 6,7-dicyano-3-(4′-fluorophenyl)-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (10d). Yield 0.31 g, 1.03 mmol (86%); mp 302–304 °C. IR (Nujol mull) 2239 (w), 2210 (s), 1596 (s), 1552 (s), 1519 (s) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=7.19 (s, 4H), 7.38 (t, J=9.0 Hz, 2H), 7.83 (dd, J=9.0, 4.8 Hz, 2H), 8.58 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ=92.5, 113.8, 114.1, 116.1 (d, J=22.9 Hz), 117.7, 125.1, 125.4 (d, J=8.6 Hz), 131.1, 143.7, 150.4, 160.9 (d, J=243.2 Hz), 166.9. Anal. Calcd for $C_{14}H_6N_5OF\cdot NH_3\cdot H_2O\cdot 0.5C_3H_7NO$ (350.83): C, 53.07; H, 4.17; N, 25.96. Found: C, 53.39; H, 4.30; N, 25.84.

3.7. General procedure for the synthesis of 3-aryl-6,7-dicyano-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridines (11a–d)

A solution of the ammonium salt of 3-aryl-6,7-dicyano-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (ca. 0.35 mmol) in ethanol (3 mL), water (5 mL), and acetic acid (1–1.5 mL) (for **11a–c**) or ethanol (3 mL), water (5 mL), DMF (2 mL), and trifluoroacetic acid (40 μL) (for **11d**) was stirred at room temperature. Turbidity gradually developed and after 10–30 min the solid was filtered and washed with ethanol and diethyl ether.

3.7.1. 6,7-Dicyano-3-(4′-tolyl)-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (11a). Yield 0.09 g, 0.23 mmol (84%); mp 323–324 °C. IR (Nujol mull) 2231 (s), 1603 (s), 1576 (m), 1519 (s), 1493 (s) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.40 (s, 3H), 7.42 (d, J=8.4 Hz, 2H), 7.65 (d, J=8.4 Hz, 2H), 8.95 (s, 1H), 13.2–13.8 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=20.6, 91.2, 112.8, 114.34, 115.1, 124.2, 130.0, 130.3, 131.2, 138.5, 147.5, 148.3, 162.4. Anal. Calcd for $C_{15}H_9N_5O\cdot 0.2H_2O$ (278.87): C, 64.61; H, 3.40; N, 25.11. Found: C, 64.77; H, 3.62; N, 24.76.

3.7.2. 6,7-Dicyano-3-(4′-cyanophenyl)-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (11b). Yield 0.08 g, 0.26 mmol (79%); mp 348–349 °C. IR (Nujol mull) 2235 (s), 1597 (s), 1519 (m), 1500 (m) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=8.14 (s, 4H), 9.14 (s, 1H), 12.60–14.40 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=91.8, 110.9, 112.7, 114.3, 115.5, 118.3, 124.1, 130.3, 133.9, 137.7, 146.9, 147.9, 162.7. Anal. Calcd for $C_{15}H_6N_6O\cdot 1.5H_2O$ (313.28): C, 57.51; H, 2.88. Found: C, 57.32; H, 2.93.

3.7.3. 6,7-Dicyano-3-(4′-methoxyphenyl)-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (11c). Yield 0.08 g, 0.27 mmol (82%); mp 311–312 °C. IR (Nujol mull) 2233 (s), 1590 (s), 1576 (s), 1521 (s), 1500 (s) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ=3.80 (s, 3H), 7.16 (d, J=9.0 Hz, 2H), 7.67 (d, J=9.0 Hz, 2H), 8.89 (s, 1H), 13.00–13.20 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=55.6, 91.1, 112.8, 114.4, 114.7, 115.0, 126.2, 126.4, 129.9, 147.8, 148.5, 159.4, 162.5. Anal. Calcd for $C_{15}H_9N_5O_2$ (291.27): C, 61.85; H, 3.11; N, 24.04. Found: C, 61.88; H, 3.22; N, 23.84.

3.7.4. 6,7-Dicyano-3-(4′-fluorophenyl)-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (11d). Yield 0.06 g, 0.17 mmol (50%); mp 315.5–316.5 °C. IR (Nujol mull) 2227 (s), 1650 (s), 1593 (s), 1521 (s), 1500 (m) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=7.49 (t, J=8.7 Hz, 2H), 7.84 (dd, J=8.7, 4.8 Hz, 2H), 8.96 (s, 1H), 13.2–14.0 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=91.3, 112.8, 114.4, 115.2, 116.6 (d, J=22.9 Hz), 127.0 (d, J=8.8 Hz), 130.0, 130.1 (d, J=2.8 Hz), 147.7, 148.4, 161.8 (d, J=244.9 Hz), 162.6. Anal. Calcd for $C_{14}H_6N_5OF\cdot C_3H_7NO$ (352.33): C, 57.95; H, 3.72; N, 23.85. Found: C, 58.08; H, 3.84; N, 23.67.

3.8. Synthesis of methyl 2-[5-amino-(4′-fluorophenyl)-imidazol-4-yl]-1,2-dicyanocarboxylate (9d)

A solution of 5-amino-4-cyanoformimidoyl-(4′-fluorophenyl)imidazole **1d** (0.10 g, 0.44 mmol) in acetonitrile (2 mL) and diethyl ether (20 mL) was combined with methyl cyanoacetate (0.06 g, 0.60 mmol) while the reaction mixture was kept stirring in an ice bath. The solution was allowed to stand at −10 °C for 24 h, when the solvent was partially removed in the rotary evaporator. Addition of ethanol (10 mL) led to an orange solid that was filtered and washed with diethyl ether to give the title compound (0.05 g, 36%) as a red solid; mp 253–255 °C. IR (Nujol mull) 2219 (m), 2202 (m), 1707 (s), 1629 (s), 1541 (s) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.77 (s, 3H), 7.18 (s, 2H), 7.46 (t, J=9.0 Hz, 2H), 7.60 (dd, J=9.0, 4.8 Hz, 2H), 7.77 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=52.6, 115.3, 116.5, 117.0 (d, J=23.2 Hz), 122.8, 129.1 (d, J=9.5 Hz), 137.0, 148.4, 162.5 (d, J=245.0 Hz), 163.0. Anal. Calcd for $C_{15}H_{10}N_5O_2F$ (313.28): C, 57.88; H, 3.24; N, 22.50. Found: C, 57.61; H, 3.55; N, 22.46.

3.9. Cyclization of methyl 2-[5-amino-(4′-fluorophenyl)-imidazol-4-yl]-1,2-dicyanocarboxylate (9d)

DBU (0.05 g, 0.34 mmol) was added to a suspension of imidazole **9d** (0.03 g, 0.10 mmol) in ethanol (5 mL) and the mixture was refluxed for 1 h. A precipitate was formed on cooling and was filtered and washed with ethanol to give the DBU salt of 6,7-dicyano-3-(4′-fluorophenyl)-5-oxo-4,5-dihydro-3*H*-imidazo[4,5-*b*]pyridine (0.03 g, 0.82 mmol, 82%) as a yellow solid; mp 227–229 °C. IR (Nujol mull) 2219 (m), 2202 (m), 1707 (s), 1629 (s), 1541 (s) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.50–1.70 (m, ½ 6H), 1.90 (m, ½ 2H), 2.61 (m, ½ 2H), 3.23 (m, ½ 2H), 3.46 (t, J=5.7 Hz, ½ 2H), 3.53 (m, ½ 2H), 7.44 (t, J=9.0 Hz, 2H), 7.80 (dd, J=9.0, 4.5 Hz, 2H), 8.76 (s, 1H), 9.60 (s, ½ 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=18.9 (DBU), 23.4 (DBU), 25.9 (DBU), 28.3 (DBU), 31.8 (DBU), 37.7 (DBU), 47.9 (DBU), 53.4 (DBU), 91.9, 113.3, 114.6, 116.4 (d, J=23.0 Hz), 126.2 (d, J=9.0 Hz), 127.4, 130.6 (d, J=2.6 Hz), 145.6, 149.5, 161.3 (d, J=243.9 Hz), 164.6 (DBU), 165.4. Anal. Calcd for $C_{14}H_6N_5OF\cdot 0.5(C_9H_{16}N_2)\cdot 0.5H_2O$ (364.36): C, 60.98; H, 4.12; N, 23.08. Found: C, 61.17; H, 3.80; N, 23.39.

3.10. Reaction of 5-amino-4-cyanoformimidoyl-1-(4′-fluorophenyl)imidazole with acetylacetone

Acetylacetone (5 mL) was added to a solution of 5-amino-4-cyanoformimidoyl-1-(4′-fluorophenyl)imidazole **1d** (0.12 g, 0.52 mmol) in acetonitrile (10 mL) and the mixture was stirred at room temperature for 2 days. The solid suspension was filtered and washed with diethyl ether. The white solid was identified as 6-carbamoyl-2-methyl-9-(4′-fluorophenyl)purine **14** (0.10 g, 69%); mp 298–299 °C. IR (Nujol mull) 1712 (s), 1575 (s), 1520 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=2.74 (s, 3H), 7.50 (t, J=8.7 Hz, 2H), 7.92 (dd, J=8.7, 4.8 Hz, 2H), 8.06 (s, 1H), 8.35 (s, 1H), 9.00 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=25.6, 116.5 (d, J=22.8 Hz), 126.2 (d, J=8.7 Hz), 129.1, 130.5, 146.4, 148.1, 153.5, 161.4 (d, J=244.2 Hz), 161.5, 164.3. Anal. Calcd for $C_{13}H_{10}N_5OF\cdot 0.2H_2O$ (274.86): C, 56.82; H, 3.78; N, 25.49. Found: C, 57.24; H, 3.91; N, 25.26.

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References and notes

1. Arvanitis, A. G.; Rescinito, J. T.; Arnold, C. R.; Wilde, R. G.; Cain, G. A.; Sun, J. H.; Yan, J. S.; Teleha, C. A.; Fitzgerald, L. W.; McElroy, J.; Zaczek, R.; Hartig, P. R.; Grossman, S.; Arneric, S. P.; Gilligan, P. J.; Olson, R. E.; Robertson, D. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 125.
2. (a) Temple, C.; Rose, J. D.; Comber, R. N.; Rener, G. A. *J. Med. Chem.* **1987**, *30*, 1746; (b) Cristalli, G.; Vittori, S.; Eleuteri, A.; Grifantini, M.; Volpini, R.; Lupidi, G.; Capolongo, L.; Pesenti, E. *J. Med. Chem.* **1991**, *34*, 2226.
3. (a) Cristalli, G.; Vittori, S.; Eleuteri, A.; Volpini, R.; Camaioni, E.; Lupidi, G.; Mohmoud, N.; Bevilacqua, F.; Palu, G. *J. Med. Chem.* **1995**, *38*, 4019; (b) Cundy, D. J.; Holan, G.; Otaegui, M.; Simpson, G. W. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 669.
4. Temple, C. *J. Med. Chem.* **1990**, *33*, 656.
5. Bukowski, L.; Janowiec, M. *Pharmazie* **1989**, *44*, 267.
6. (a) Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Siegel, P. K. S.; Chang, R. S.; Lotti, V. J.; Faust, K. A.; Chen, T. B.; Schorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem.* **1991**, *34*, 2919; (b) Kim, D.; Mantlo, N. B.; Chang, R. S.; Kivlighn, S. D.; Greenlee, W. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 41; (c) Cappelli, A.; Mohr, G. P.; Gallelli, A.; Rizzo, M.; Anzini, M.; Vomero, S.; Mennuni, L.; Ferrari, F.; Makovec, F.; Menziani, M. C.; De Benedetti, P. G.; Giorgi, G. *J. Med. Chem.* **2004**, *47*, 2574; (d) Cappelli, A.; Mohr, G. P.; Giuliani, G.; Galeazi, S.; Anzini, M.; Mennuni, L.; Ferrari, F.; Makovec, F.; Kleinrath, E. M.; Langer, T.; Valoti, M.; Giorgi, G.; Vomero, S. *J. Med. Chem.* **2006**, *49*, 6451.
7. Krasavin, M.; Kobak, V. V.; Bondarenko, T. Y.; Kravchenko, D. V. *Heterocycles* **2005**, *65*, 2189.
8. Yang, D. L.; Fokas, L. J. Z.; Yu, L. B.; Baldino, C. M. *Synthesis* **2005**, *1*, 47.
9. Khanna, I. K.; Weier, R. M.; Lentz, K. T.; Swenton, L.; Lankin, D. C. *J. Org. Chem.* **1995**, *60*, 960.
10. Al-Shaar, A. H. M.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2779.
11. Penning, T. D.; Chandrakumar, N. S.; Desai, B. N.; Djuric, S. W.; Gasiecki, A. F.; Malecha, J. W.; Miyashiro, J. M.; Russel, M. A.; Askonas, L. J.; Gierse, J. K.; Harding, E. I.; Highkin, M. K.; Kachur, J. F.; Kim, S. H.; Villani-Price, D.; Pyla, E. Y.; Ghoreishi-Haack, N. S.; Smith, W. G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1137.
12. (a) Alves, M. J.; Booth, B. L.; Freitas, A. P.; Proença, M. F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 913; (b) Booth, B. L.; Dias, A. M.; Proença, M. F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2119; (c) Alves, M. J.; Booth, B. L.; Proença, M. F. *J. Heterocycl. Chem.* **1994**, *31*, 345; (d) Booth, B. L.; Coster, R. D.; Proença, M. F. *Synthesis* **1988**, 389; (e) Alves, M. J.; Booth, B. L.; Carvalho, M. A.; Pritchard, R. G.; Proença, M. F. *J. Heterocycl. Chem.* **1997**, 739; (f) Al-Azmi, A.; Booth, B. L.; Carpenter, R. A.; Carvalho, M. A.; Marrelec, E.; Pritchard, R. G.; Proença, M. F. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2532; (g) Booth, B. L.; Cabral, I. M.; Dias, A. M.; Freitas, A. P.; Matos-Beja, A. M.; Proença, M. F.; Ramos-Silva, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1241; (h) Carvalho, M. A.; Esteves, T. M.; Proença, M. F.; Booth, B. L. *Org. Biomol. Chem.* **2004**, *2*, 1019; (i) Carvalho, M. A.; Álvares, Y.; Zaki, M. E.; Proença, M. F.; Booth, B. L. *Org. Biomol. Chem.* **2004**, *2*, 2340.
13. (a) Dias, A. M.; Cabral, I. M.; Proença, M. F.; Booth, B. L. *J. Org. Chem.* **2002**, *67*, 5546; (b) Zaki, M. E.; Proença, M. F.; Booth, B. L. *J. Org. Chem.* **2003**, *68*, 276.
14. Zaki, M. E. A.; Proença, M. F.; Booth, B. L. *Synlett* **2005**, 2429.
15. *Handbook of Chemistry and Physics*, 76th ed.; Lide, D. R., Editor-in-chief, Ed.; CRC: New York, NY, 1995.
16. Bordwell, F. G.; Van Der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1883.
17. Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.
18. Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327.
19. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
20. Tuberculosis Antimicrobial Acquisition & Coordinating Facility, Southern Research Institute, Birmingham, Alabama, USA.
21. Alves, M. J.; Booth, B. L.; Al-Duaij, O. K.; Eastwood, P.; Nezhat, L.; Proença, M. F.; Ramos, A. S. *J. Chem. Res., Synop.* **1993**, 402; *J. Chem. Res., Miniprint* **1993**, 2701.
22. Slätt, J.; Romero, I.; Bergman, J. *Synthesis* **2004**, 2760.