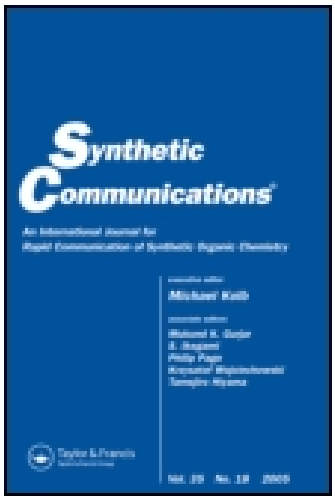

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SYNTHESIS OF 5-AMINO-1-ARYL-4-CYANOIMIDAZOLES FROM *N*-ARYL-*N′*-(1,2-DICYANOVINYL)-FORMAMIDINES

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ABSTRACT

The aryl-(*Z*)-*N*-[2-amino-1,2-dicyanovinyl]formamidine cyclize in the presence of base to give a 1,5-diamino-4-cyanoimidazole or a 1,5-diamino-4-(cyanoformimidoyl)imidazole, depending on the reaction conditions and the nature of the base used to induced cyclization.

5-Amino-4-cyanoimidazoles have long been recognized as useful synthetic precursors for compounds such as a series of biologically active purines and their derivatives, but there is no simple, general synthesis available for 1-aryl derivatives of these compounds.

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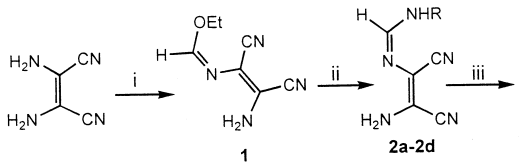
Preparation of 5-amino-4-cyano-l-(*p*-aminosulfonylphenyl)imidazole was reported via a multistep synthesis from the corresponding 1-methyl derivative.[1] Frank and Zeller have described the synthesis of a number of 1-aryl and 1-heteroaryl derivatives in low to moderate yield by reaction of the corresponding ethyl *N*-substituted formimidates with 2-aminomalononitrile toluene-*p*-sulfonate in acetic acid.[2] We have been developing new routes to 5-amino-1-aryl-4-cyanoimidazoles (**2**) from corresponding cyanoformimidoyl imidazoles (**3**) by treatment with aqueous KOH solution.[3]

The same compounds (**3**) can also be synthesised directly from the corresponding amidines (**2**) under similar strongly basic conditions. We thus attempted to cyclise the aromatic amidines (**2a–2d**) to obtain compounds of type (**3a–3d**), which would be important intermediates for the synthesis of a range of 9-arylpurines and 9-aryl-1,2-dihydropurines.[4,5]



2, 3		yield (%) of 3
a	R=2-ClC$_6$H$_4$CH$_2$-	85
b	R=3,4-(CH$_3$O)$_2$C$_6$H$_3$CH$_2$-	90
c	R=3,4-(CH$_3$O)$_2$C$_6$H$_3$-	89
d	R=4-CH$_3$OC$_6$H$_4$-	93

Scheme 1. Reagents and conditions; i, $HC(OEt)_3$, dioxane, heat; ii, RNH_2, $PhNH_3^+Cl^-$, room temp., 3–4 h; iii, 1 mol dm^{-3} KOH, aq. room temp.

The preparation of 5-amino-1-aryl-4-cyanoimidazoles (**3a–3d**) were attempted from the corresponding amidines (**2a–2d**) in the presence of an aqueous potassium hydroxide solution (1 M) at room temperature. Imidate (**1**) was prepared in high yield from diaminomaleonitrile and triethyl orthoformate, according to a previously described procedure.[6–8] Having obtained the imidate (**1**) in good yield (94%) it was then treated with aryl or benzylamine in a 1 : 1 molar ratio in ethanol in the presence of a catalytic amount of anilinium hydrochloride.[4] The cyanoimidazoles (**3a–3d**) were isolated in good yields.

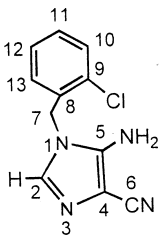
Compounds (**3a–3d**) were recrystallised from mixture of ethanol/methanol (1 : 1) and gave pale yellow to off white crystals respectively.

These were fully characterized by microanalysis, IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The infrared spectrum confirmed the presence of the NH and C=N stretching vibrations within the region of 3460–3140 (3–4 bands), and 1655–1650 cm^{-1} respectively. The infrared spectrum also showed a sharp absorption band within the range of 2200–2240 cm^{-1} for the C≡N stretching vibration. In the ^{1}H NMR spectra of the isolated 5-amino-1-aryl-4-cyanoimidazoles, the primary amine protons were observed in the region of 6.10–6.58 ppm and in several cases the assignment were confirmed by D_2O exchange. The proton of the imidazole ring (H-2) appeared as a sharp singlet in the range of 7.41–7.50 ppm. The ^{13}C NMR spectra of the compounds (**2a–2d**) had the expected number of peaks. The C-2 carbon of the imidazole ring appeared in the region of 136.7–137.7 ppm.

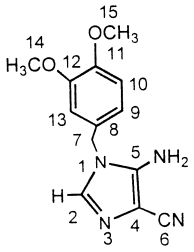
EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Hitachi-Perkin-Elmer R24B (60 MHz) or Bruker XL 300 (300 MHz) instruments (with J-values given in hertz), ^{13}C NMR spectra (with DEPT 135) either on a Bruker WP80 or XL300 instrument, and IR spectra on a Shimadzu IR-435 spectrophotometer. Mass spectra were recorded on a Kratos Concept instrument. The melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected.

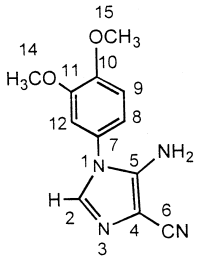
General procedure for the preparation of the 5-Amino-1-aryl-4-cyanoimidazoles (3a–3d). A suspension of the corresponding aryl-(Z)-*N*-[2-amino-1,2-dicyanovinyl]formamidine (**2a–2d**) (1.00 g) in potassium hydroxide solution (1 M, 10 cm^3) was stirred at room temperature until TLC showed complete consumption of the starting material. The precipitated product was filtered off, washed with water (5 cm^3), followed by a mixture of dry diethyl ether/ethanol (10 : 1) and air-dried in the absence of light to give the desired products (**3a–3d**).



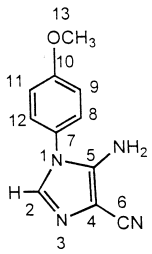
5-Amino-1-(2-chlorobenzyl)-4-cyanoimidazole (3a): Recrystallisation of the product from dry diethyl ether/ethanol (1 : 1) and air-dried in the absence of light to give white crystals of (**3a**) (0.76 g, 3.28 mmol, 85%). m.p. 112–114°C (decomp.). [Found: C, 56.3; H, 4.0; N, 23.8; Cl, 14.8. $C_{11}H_9N_4Cl$ requires C, 56.8; H, 3.87; N, 24.1; Cl, 1.52%]; *m/z* (FAB) 233 $(M+1)^+$ 100%, 232 $(M)^+$ 34%, 192 $[(M-1)\text{-}CN_2H_2]^+$ 34%, 154 $[(M-1)\text{-}C_3H_2N_3]^+$ 6.7%, 136 (32%), 125 (54%); δ_H (300 MHz, d_6-DMSO) 5.42 (s, 2H, CH_2), 6.58 (s, 2H, NH_2), 7.07 (dd, 1H, $^3J_{12,13}$ 7 Hz, $^4J_{11,13}$ 1.5 Hz, H13), 7.42 (s, 1H, H2), 7.63–7.68 (overlapping 2 × dt, 2H, $^4J_{11,13}$ 2 Hz, $^3J_{11,10}$ 8 Hz, H11 and H12), 7.85 (dd, 1H, $^3J_{10,11}$ 7 Hz, $^4J_{10,12}$ 1.5 Hz, H10) ppm: δ_C (75 MHz, d_6-DMSO) 48.1 (C7, by DEPT 135), 94.2 (C4), 121.3 (C6), 131.5 (C12), 133.3 (C13), 133.4 (C11), 135.7 (C10), 136.8 (C9), 137.7 (C2), 139.6 (C8), 151.9 (C5) ppm; ν_{max} (Nujol mull) 3440m, 3380s, 3330s, 3200s, (N-H str.), 2220s, (CH str.), 1655s (C=N str.), 1580s (N-H bend), 1530s, 1480s, 1440s, 1360s, 1280s, 1210s, 1065s, 1060s, 980s, 860m, 820m, 780s, 740m, 710m cm^1.



5-Amino-1-(3,4-dimethoxybenzyl)-4-cyanoimidazole (3b): Recrystallisation of the product from ethanol/methanol (1 : 1) give pale yellow crystals of (**3b**) (0.80 g, 3.13 mmol, 90%). m.p. 171–172.5°C (decomp.). [Found: C, 60.7; H, 5.3; N, 21.4. $C_{13}H_{14}N_4O_2$ requires C, 60.5; H, 5.4; N, 21.7%]; *m/z* (Cl, NH_3) 259 $(M+1)^+$ 21.4%, 153 $(M\text{-}C_4H_3N_4)^-$ 100%; δ_H (300 MHz, d_6-DMSO) 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.10 (s, 2H, H7), 6.42 (s, 2H, NH_2), 6.90 (dd, 1H, $^3J_{9,10}$ 8 Hz, $^4J_{9,13}$ 2 Hz, H9), 7.08 (d, 1H, $^3J_{10,9}$ 8 Hz, H10), 7.14 (d, 1H, $^4J_{13,9}$ 2 Hz, H13), 7.42 (s, 1H, H2) ppm: δ_C (75 MHz, d_6-DMSO) 50.0 (C7, by DEPT 135), 59.5 (C14 and C15 overlapping), 94.3 (C4), 115.7 and 115.9 (C10 and C13), 121.6 (C6), 123.9 (C9), 132.6 (C8), 136.7 (C2), 151.6 (C5), 152.5 and 152.8 (C11 and C12) ppm; ν_{max} (Nujol mull) 3400s, 3395m, 3220s, 3160s, 3120w (N-H str.), 2210s, 2200s (CN str.), 1655s (C=N str.), 1610s (N-H bend), 1580s, 1525s, 1265s, 1165s, 1140s, 1025s, 865s, 820m, 780s, 740m cm^{-1}.



5-Amino-1-(3,4-dimethoxyphenyl)-4-cyanoimidazole (3c): Recrystallisation of the product from ethanol/methanol (1 : 1) gave pale yellow crystals of (**3c**) (0.80 g, 3.28 mmol, 89%). m.p. 218–219°C (decomp.). [Found: C, 59.2; H, 4.6; N, 22.6. Calc. for $C_{12}H_{12}N_4O_2$ C, 59.0; H, 4.9; N, 22.9%]; *m*/*z* (Cl, NH_3) 245 $(M+1)^+$ 100%, 137 $(M\text{-}C_4H_3N_4)^+$ 3%; δ_H (300 MHz, d_6-DMSO) 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.30 (s, 2H, NH_2), 7.14 (dd, 1H, $^3J_{8,9}$ 8 Hz, $^4J_{8,12}$ 2 Hz H8), 7.20 (d, 1H, $^4J_{12,8}$ 2 Hz, H12), 7.28 (d, 1H, $^3J_{9,8}$ 8 Hz, H9), 7.50 (s, 1H, H2) ppm; δ_C (75 MHz, d_6-DMSO) 59.6 and 59.7 (C13 and C14), 94.3 (C4), 113.6 and 115.9 (C9 and C12), 121.1 (C6), 121.6 (C8), 130.4 (C7), 136.6 (C2), 151.4 (C5), 152.9 and 153.1 (C10 and C11) ppm; ν_{max} (Nujol mull) 3460s, 3385m, 3220s, 3140s, (N-H str.), 2220s, 2200s (CN str.), 1650s (C=N str.), 1615s (N-H bend), 1595s (N-H bend), 1525s, 1255s, 1160s, 1040s, 880s, 780s cm^{-1}.



5-Amino-1-(4-methoxybenzyl)-4-cyanoimidazole (3d): Recrystallisation of the product from ethanol/methanol (1 : 1) gave white crystals of (**3d**) (0.82 g, 3.83 mmol, 0.93%). m.p. 167–168°C (decomp.). [Found: C, 61.4; H, 4.7; N, 25.9. Calc. for $C_{11}H_{10}N_4O$ C, 61.7; H, 4.7; N, 26.2%]; *m*/*z* (FAB) 214 $(M)^+$ 100%; δ_H (300 MHz, d_6-DMSO) 3.81 (s, 3H, OCH_3), 6.10 (s, 2H, NH_2), 7.15 (d, 2H, $^3J_{9,8}$ 9 Hz, H9 and H11), 7.39 (d, 2H,

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$^3J_{12,11}$ 9 Hz, H8 and H12), 7.41 (s, 1H, H2) ppm; δ_C (75 MHz, d_6-DMSO) 59.6 (C13), 94.7 (C4), 119.1 (C9 and C11), 121.1 (C6), 130.5 (C7), 131.1 (C8 and C12), 136.8 (C2), 151.6 (C5), 163.4 (C10) ppm; ν_{max} (Nujol mull) 3380m, 3340s, 3200s, 3180m, (N-H str.), 2240s, 2200s (CN str.), 1655s (C=N str.), 1595s (N-H bend), 1530s, 1270s, 1040s, 970s, 860s, 815s cm^{-1}.

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