

Synthesis of 5-amino-1-aryl-4-cyanoimidazoles from formamidines under solvent-free condition

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ABSTRACT

The aryl-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidine 2 cyclize in solvent-free conditions and in the presence of a base to give a 5-amino-1-aryl-4-cyanoimidazoles 3. Silica sulfuric acid as an efficient and reusable heterogeneous catalyst has been used for the preparation of amidines 2 from formimidate 1 through reaction with aromatic amines at room temperature and in good to excellent yields. All these derivatives were fully characterized by spectroscopic data.

Keywords: Silica sulfuric acid, Heterogeneous catalyst, Imidate, Amidine, Aiaminomaleonitrile, Cyanoimidazole.

1. Introduction

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 and available synthesis method for 1-aryl derivatives of these compounds [1-4]. Preparation of 5-amino-4-cyano-1-(*p*-aminosulfonylphenyl)imidazole was reported via a multistep synthesis from the corresponding 1-methyl derivative [5]. 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-aminomalonitrile toluene-*p*-sulfonate in acetic acid [6].

We have been interested in the chemistry of diaminomaleonitrile (DAMN) and its derivatives, in particular, ethyl-2-(2-amino-1,2-dicyanovinyl) formimidate 1 which can be prepared in good yield from the reaction between DAMN and triethyl orthoformate in 1,4-dioxane [7-10]. From our previous work in this area, we found that 1 would be a useful starting material for the preparation of new *N*-aryl-*N'*-[2-amino-1,2-dicyanovinyl]formamidines 2. Using procedures developed in our laboratories it was

envisaged that these could be readily converted into 5-amino-1-aryl-4-(cyanoformimidoyl)-1H-imidazoles 3 [7-14], which are expected to be useful precursors for the preparation of new 6-carbamoyl-1,2-dihydropurines and 6- substituted purines [7,12]. In addition, reactions of compound 2 could provide a simple route to synthesizing the desired 5-amino-1-aryl-4-cyanoimidazoles 3.

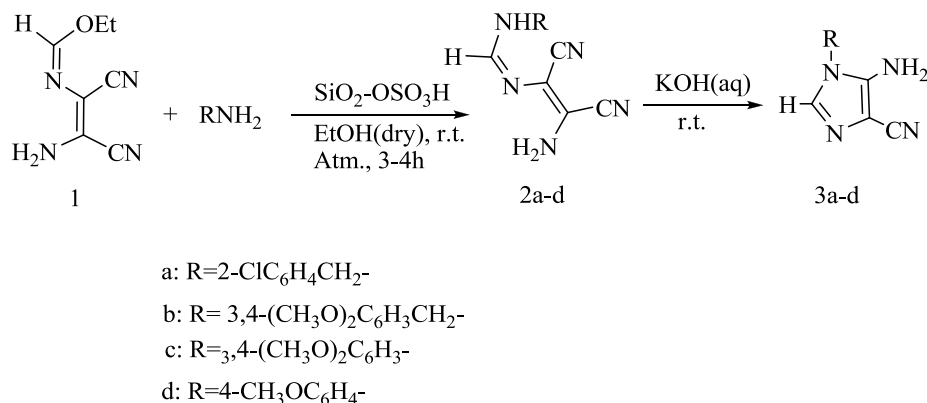
2. Experimental

High-resolution ¹H NMR (300 MHz), ¹³C NMR (75 MHz) spectra were obtained via a Bruker 500 DRX-Avance NMR spectrometer. The compounds were dissolved in deuterated DMSO as NMR solvent. IR data was obtained with a Shimadzu 470 spectrometer. Mass spectra were recorded using a GC-MS Agilent Technologies QP-5973N MSD instrument. The elemental analysis was determined on a Leco CHNS-900 analyzer. The Melting points of crystalline compounds were measured with an electrothermal melting point apparatus and have not been corrected. Purification of 1,4-dioxane and diethyl ether were refluxed with adding Na (1 % w/v) and benzophenone (0.2% w/v) under an inert atmosphere until the blue colour of the benzophenone appeared. Dry dioxane was distilled, and store over 4A molecular sieves in the dark. Typical reaction procedures and spectroscopic data for all products are described below.

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Scheme 1. Synthetic route of 5-amino-1-aryl-4-cyanoimidazoles **3a-d**.

2.1 Preparation of Ethyl(Z)-N-(2-amino-1,2-dicyanovinyl)formimidate (1, C₇H₈N₄O)

A mixture of diaminomalenitrile (1 g, 9.25 mmol) and triethyl orthoformate (1.37 mL, 1.22 g, 9.24 mmol) in dioxane (2 mL) was heated in a round bottom flask fitted with a short vigreux column, distillation head, condenser and receiver. Ethanol, mixed with dioxane, was removed continuously until the temperature in the distillation head reached 99 °C. The brown solution in the distillation pot was allowed to cool and was then filtered. A white, needle-shaped crystal (1.42 g, 8.70 mmol, 94%) was obtained after recrystallization from dichloromethane and petroleum ether. m.p. 132-133 °C (decomp.), [lit., 135-137 °C]; [Found: C, 51.3; H, 4.8; N, 34.2. Calc. for C₇H₈N₄O: C, 51.2; H, 4.9; N, 34.1%]; m/z (EI) 165 (M+1)⁺ 94.2%, 119 (M-OC₂H₅)⁺ 32.9%, 81 [(M+1)-C₄H₆NO]⁺ 96.3%, 29 [(M+1)-C₆H₆N₃O]⁺ 100%; ¹H NMR (300 MHz, DMSO-*d*₆, ppm) δ: 1.30 (t, 3H, ³J_{6,7}= 7 Hz, H7), 4.30 (q, 2H, ³J_{7,6}= 7Hz, H6), 7.00 (br. s, 2H, NH₂), 7.97 (s, 1H, H5); IR (Nujol, ν_{max}, cm⁻¹): 3410 (m), 3300 (s), 3160 m (N-H str.), 2220 (s), 2200 (s, C=N str.), 1600 (m, N-H bend), 1470 (m), 1360 (s), 1260 (m), 1130 (s), 800 (m) and 750 (m).

2.2 General procedure for the preparation of the N-Aryl-N'-(2-amino-1,2-dicyanovinyl)formamidines 2a-d

The amines (1.01g, 6.07 mmol) were added to a suspension of 1 (1.00 g, 6.09 mmol) in dry ethanol, which contained silica sulfuric acid (0.01 g) for these reactions. The mixtures were stirred at room temperature until TLC (9:1 chloroform/ethanol eluant) showed that all the formimidate had disappeared (usually 3 to 4 h) and the catalyst recovered by filtration, was washed with ethanol (10 mL), dried at room temperature and reused four times for the same reaction. The amidines were isolated by filtration and the filtrate was evaporated to furnish the crude product which was further purified by usual crystallization

procedure in absolute ethanol. In most cases the products 2a-d were pale green to white. The precipitates were washed with dry diethyl ether and were dried under vacuum to give the analytically pure products 2a-d.

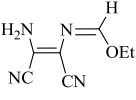
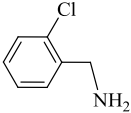
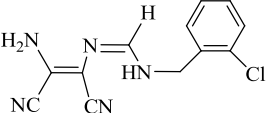
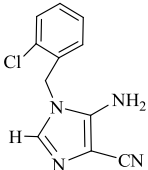
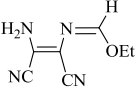
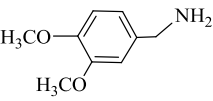
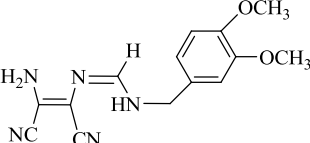
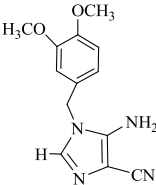
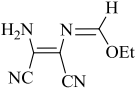
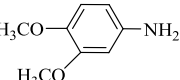
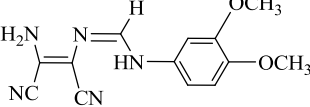
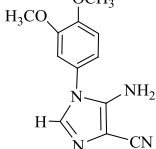
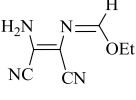
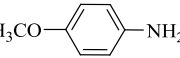
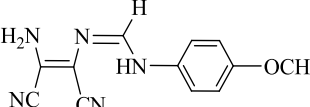
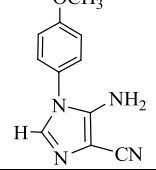
2.3 General procedure for the preparation of the 5-amino-1-aryl-4-cyanoimidazoles 3a-d

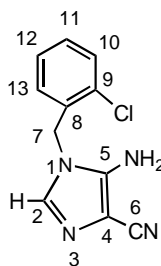
A suspension of the corresponding aryl-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidine 2a-d (1.00 g) in potassium hydroxide solution (1 M, 10 mL) was stirred at room temperature for approximately 1 h until TLC showed complete consumption of the starting material. The precipitated product was filtered off, washed with water (5 mL), 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-d. The yields of these reactions were 85-93%.

5-Amino-1-(2-chlorobenzyl)-4-cyanoimidazole 3a

Recrystallization of the product from dry diethyl ether/ethanol (1:1) and air-dried in the absence of light gave white crystals of 3a (0.76 g, 3.28 mmol, 85%). m.p. 112-114 °C (decomp.) [11]; [Found: C, 56.3; H, 4.0; N, 23.8; Cl, 14.8. Calc. for C₁₁H₉N₄Cl: C, 56.8; H, 3.87; N, 24.1, Cl, 15.2%]; m/z (FAB) 233 (M+1)⁺ 100%, 232 (M)⁺ 34%, 192 [(M-1)-CN₂H₂]⁺ 34%, 154 [(M-1)-C₃H₂N₃]⁺ 6.7%, 136 (32%), 125 (54%); ¹H NMR (300 MHz, DMSO-*d*₆, ppm) δ: 5.42 (s, 2H, CH₂), 6.58 (s, 2H, NH₂), 7.07 (dd, 1H, ³J_{12,13}= 7 Hz, ⁴J_{11,13}= 1.5Hz, H13), 7.42 (s, 1H, H2), 7.63-7.68 (overlapping 2x dt, 2H, ⁴J_{11,13}= 2Hz, ³J_{11,10}= 8Hz, H11 & H12), 7.85 (dd, 1H, ³J_{10,11}= 7Hz, ⁴J_{10,12}= 1.5Hz, H10). ¹³C NMR (75 MHz, DMSO-*d*₆, ppm) δ: 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; IR (Nujol, ν_{max}, cm⁻¹): 3440 (m), 3380 (s), 3330 (s), 3200 (s, N-H str.), 2220 (s, CN str.), 1655 (s, C=N str.),

Table 1: Structures of imidazole **3a-d** with the usage of amidine and saturated solution of potassium hydroxide.

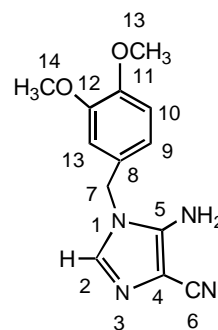
Entry	Substrate (imidate)	Amine	Formamidine (2a-d)	Product Imidazole (3a-d)	m.p. (°C)	Reaction Time (min)	Yield (%)
a					112-114	60	85
b					171-173	48	90
c					218-219	45	89
d					167-168	50	93



1580 (s, N-H bend), 1530 (s), 1480 (s), 1440 (s), 1360 (s), 1280 (s), 1210 (s), 1065 (s), 1060 (s), 980 (s), 860 (m), 820 (m), 780 (s), 740 (m), 710 (m).

5-Amino-1-(3,4-dimethoxybenzyl)-4-cyanoimidazole 3b

Recrystallization of the product from diethyl ether/ethanol (1:1) gave pale yellow crystals of **3b** (0.80 g, 3.13 mmol, 90%). m.p. 171-173 °C (decomp.) [11]; [Found: C, 60.7; H, 5.3; N, 21.4 . Calc. for C₁₃H₁₄N₄O₂: C, 60.5; H, 5.4; N, 21.7%]; m/z (CI, NH₃)

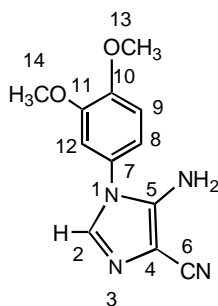


259 (M+1)⁺ 21.4%, 153 (M-C₄H₃N₄)⁺ 100%; ¹H NMR (300 MHz, DMSO-*d*₆, ppm) δ: 3.88 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 5.10 (s, 2H, H7), 6.42 (s, 2H, NH₂), 6.90 (dd, 1H, ³J_{9,10}= 8Hz, ⁴J_{9,13}= 2Hz, H9), 7.08 (d, 1H, ³J_{10,9}= 8Hz, H10), 7.14 (d, 1H, ⁴J_{13,9}= 2Hz, H13), 7.42 (s, 1H, H2). ¹³C NMR (75 MHz, DMSO-*d*₆, ppm) δ: 50.0 (C7, by DEPT 135), 59.5 (C14 & C15 overlapping), 94.3 (C4), 115.7 and 115.9 (C10 & C13), 121.6 (C6), 123.9 (C9), 132.6 (C8), 136.7 (C2), 151.6 (C5), 152.5 and 152.8 (C11 & C12). IR (Nujol, ν_{max}, cm⁻¹): 3400 (s), 3395 (m), 3220 (s), 3160 (s), 3120 (w),

N-H str.), 2210 (s), 2200 (s, C=N str.), 1610 (s, N-H bend), 1580 (s), 1525 (s), 1265 (s), 1165 (s), 1140 (s), 1025 (s), 865 (s), 820 (m), 780 (s), 740 (m).

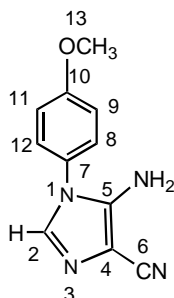
5-Amino-1-(3,4-dimethoxyphenyl)-4-cyanoimidazole 3c

Recrystallization of the product from diethyl ether/ethanol (1:1) gave pale yellow crystals of 3c (0.80 g, 3.28 mmol, 89%). m.p. 218-219 °C (decomp.) [11]; [Found: C, 59.2; H, 4.6; N, 22.6. Calc. for C₁₂H₁₂N₄O₂ C, 59.0; H, 4.9; N, 22.9%]; m/z (CI, NH₃) 245 (M+1)⁺ 100%, 137 (M-C₄H₃N₄)⁺ 3%; ¹H NMR (300 MHz, DMSO-*d*₆, ppm) δ: 3.96 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 6.30 (s, 2H, NH₂), 7.14 (dd, 1H, H12), 7.28 (d, 1H, ³J_{9,8}= 8Hz, H9), 7.50 (s, 1H, H2), ¹³C NMR (75 MHz, DMSO-*d*₆, ppm) δ: 59.6 and 59.7 (C13 & C14), 94.3 (C4), 113.6 and 115.9 (C9 & C12), 121.1 (C6), 121.6 (C8), 130.4 (C7), 136.6 (C2), 151.4 (C5), 152.9 and 153.1 (C10 & C11); IR (Nujol, ν_{max}, cm⁻¹): 3460 (s), 3385 (m), 3220 (s), 3140 (s, N-H str.), 2220 (s), 2200 (s, CN str.), 1615 (s, N-H bend), 1595 (s, N-H bend), 1525 (s), 1255 (s), 1160 (s), 1040 (s), 880 (s), 780 (s).



5-Amino-1-(4-methoxyphenyl)-4-cyanoimidazole 3d

Recrystallization of the product from diethyl ether/ethanol (1:1) gave white crystals of 3d (0.82 g, 3.83 mmol, 0.93%). m.p. 167-168 °C (decomp.) [11]; [Found: C, 61.4; H, 4.7; N, 25.9. Calc. for C₁₁H₁₀N₄O: C, 61.7; H, 4.7; N, 26.2%]; m/z (FAB) 214 (M)⁺ 100%; ¹H NMR (300 MHz, DMSO-*d*₆, ppm) δ: 3.81 (s, 3H, OCH₃), 6.10 (s, 2H, NH₂), 7.15 (d, 2H, ³J_{9,8}= 9Hz, H9 & H11), 7.39 (d, 2H, ³J_{12,11}= 9Hz, H8 & H12),



7.41 (s, 1H, H2); ¹³C NMR (75 MHz, DMSO-*d*₆, ppm) δ: 59.6 (C13), 94.7 (C4), 119.1 (C9 & C11), 121.1 (C6), 130.5 (C7), 131.1 (C8 & C12), 136.8 (C2), 151.6 (C5), 163.4 (C10); IR (Nujol, ν_{max}, cm⁻¹): 3380 (m), 3340 (s), 3200 (s), 3180 (m, N-H str.), 2240 (s), 2200 (s, CN str.), 1595 (s, N-H bend), 1530 (s), 1270 (s), 1040 (s), 970 (s), 860 (s), 815 (s).

3. Results and Discussion

Recently, we have developed new routes to 5-amino-1-aryl-4-cyanoimidazoles 3 from corresponding aryl-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidines 2 in the presence of an aqueous potassium hydroxide solution (1M) at room temperature [3,7-13]. We thus attempted to cyclize the aromatic amidines 2a-d to obtain compounds of type 3a-d, which would be important intermediates for the synthesis of a range of 9-arylpurines and 9-aryl-1,2-dihydropurines.

Imidate 1 was prepared in high yield from diaminomaleonitrile and triethyl orthoformate, according to a previously described procedure [6-8].

In recent years, there has been considerable growth of interest in the catalysis of organic reactions by solid acid catalysts. Solid acid catalysts provide numerous opportunities for recovering and recycling catalysts from reaction environments. These features can lead to the improvement of the processing steps, better economical processes, and environmentally friendly industrial manufacturing.

Having obtained the imidate 1 in good yield, it was then treated with arylamine and benzylamine in a 1:1 molar ratio in ethanol in the presence of a catalytic amount of silica sulfuric acid as an efficient and reusable heterogeneous catalyst [13-17] for this reaction (Scheme 1, Table 1). Silica sulfuric acid was prepared from the reaction of silica gel with chlorosulfonic acid [15-20]. The reaction mixture was stirred under an inert atmosphere at room temperature. A solution 2 was obtained and within 20 minutes a white solid precipitated out. The products 2a-d were filtered off after 3-4 hours. It was washed with diethyl ether and was found to be pure by TLC, ¹H NMR, ¹³C NMR and IR spectroscopy.

When a saturated solution of potassium hydroxide in ethanol was added to a suspension of the amidines 2a-d in an alcohol at room temperature, the corresponding 5-amino-1-aryl-4-cyanoimidazoles 3a-d were formed in good yields (85-93%). The products 3a-d were filtered off after approximately 1h until TLC showed complete consumption of the starting material. Compounds 3a-d were recrystallized from a mixture of diethyl ether/ethanol (1:1). These products were fully characterized by microanalysis, IR, ¹H and ¹³C NMR spectroscopy and mass spectrometry [11]. 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 ^1H 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 assignments 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 3a-d had the expected number of peaks. The C-2 carbon of the imidazole ring appeared in the region of 136.7-137.7 ppm.

4. Conclusion

In summary, an efficient protocol for the preparation of imidazole derivatives was described. The reactions were carried out at room temperature and the corresponding products were obtained in good to excellent yield. Also, the catalyst could be successfully recovered and reusable.

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