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## Synthesis of 5-Amino-4-cyanoformimidoylimidazoles and 5-Amino-4-cyanoimidazoles from Amidines

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*Imidazole and formimidoylimidazole derivatives have been synthesized in high yields by a reaction between amidine and a strong or weak base depending on reaction conditions and mainly on the nature of the base used to induced cyclization. All compounds have been characterized by spectroscopic data.*

**Keywords** Amidine; anilinium hydrochloride; cyanoimidazole; diaminomaleonitrile; formimidoylimidazole; imidate

### 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,<sup>1–5</sup> but there is no simple, general synthesis available for 1-aryl derivatives of these compounds.

In 1976, Sen and Ray<sup>6</sup> reported the synthesis of 5-amino-4-cyano-1-(3-diethylaminopropyl)imidazole and 5-amino-4-cyano-1-benzylimidazole via a multistep synthesis.

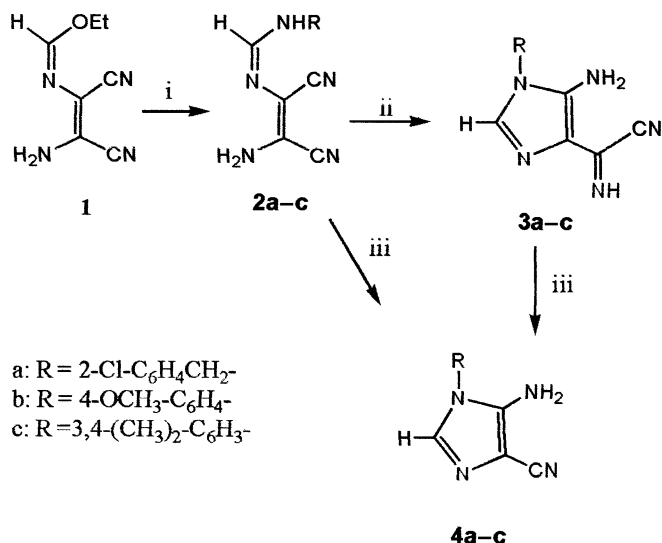
### RESULT AND DISCUSSION

The compound **4** can be synthesised directly from the corresponding amidine **2** under strongly basic conditions or formimidoyl-imidazole under a weakly basic condition and then a strong base.<sup>7–11</sup> We thus attempted to cyclize amidines **2a–c** to obtain compounds of type **3a–c** and **4a–c**, which would be important intermediates for the synthesis of a range of 9-aryl purines and 9-aryl-1,2-dihydropurines.<sup>12–14</sup>

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Imidate **1** was prepared in a high yield from diaminomaleonitrile and triethyl orthoformate, according to a previously described procedure.<sup>8–10</sup> Having obtained the imidate **1** in a 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<sup>9,10</sup> to give **2a–c**. The preparation of 5-amino-1-aryl-4-cyanoimidazoles **4a–c** were attempted from the corresponding amidines **2a–c** in the presence of an aqueous potassium hydroxide solution (1M) at r.t. or DBU and an aqueous potassium hydroxide solution (1M). The cyanoimidazoles **4a–c** were isolated in good yields (Scheme 1).



**SCHEME 1** Reagents and conditions; i, RNH<sub>2</sub>, ArNH<sub>3</sub><sup>+</sup>Cl<sup>-</sup>; ii, DBU, r.t.; iii, KOH (1M), r.t.

Compounds **4a–c** were recrystallized from a mixture of ethanol/methanol (1:1) and gave pale yellow to off-white crystals, respectively. These were fully characterized by TLC, IR, and <sup>1</sup>H NMR spectroscopy. The infrared spectrum confirmed the presence of the NH and C=N stretching vibrations within the region of 3400–3100 and 1660–1650 cm<sup>-1</sup>, respectively. The infrared spectrum also showed a sharp absorption band within the range of 2220–2200 cm<sup>-1</sup> for the C≡N stretching vibration. In the <sup>1</sup>H NMR spectra of the isolated 5-amino-1-aryl-4-cyanoimidazoles, the primary amine protons were observed in the region of 5.60–6.60 ppm, and in several cases the assignments were confirmed by D<sub>2</sub>O exchange. The proton of the imidazole ring appeared as a sharp singlet in the range of 7.14–7.42 ppm.

## EXPERIMENTAL

The  $^1\text{H}$  NMR spectra were recorded on Hitachi-Perkin-Elmer R24B (60 MHz) or Bruker XL 500 (500 MHz) instruments, and IR spectra were recorded on a Shimadzu IR-470 spectrophotometer. Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected.

### General Procedure for the Preparation of the 5-Amino-4-cyanoformimidoylimidazole **3a–c**

To a suspension of the corresponding aryl-(Z)-N-(2-amino-1,2-dicyanovinyl)formamidine **2a–c**<sup>7–9</sup> (1.00 g) in dry ethanol (8 mL) DBU (9 drops) was added. The mixture was stirred under an argon atmosphere at r.t. for 0.5–3 h. After this time, TLC showed that all the amidine had been consumed. The reaction mixture was then filtered, washed with dry diethyl ether, and dried under vacuum to give **3a–c**.

### 5-Amino-1-(2-chlorobenzyl)-4-cyanoformimidoylimidazole **3a**

Recrystallisation of the product from dry diethyl ether and air dried in the absence of light gave yellow crystals of **3a** (0.7 g, 2.7 mmol, 71%). m.p. 114–116°C (decomp.);  $\delta_{\text{H}}$  (500 MHz,  $d_6$ -DMSO) 5.45 (s, 2H,  $\text{CH}_2$ ), 6.60 (s, 2H,  $\text{NH}_2$ ), 6.70–6.84 (m, 4H, Ar–H), 7.20 (s, 1H, H-imidazole) 9.8 (br. s, 1H, NH) ppm:  $\nu_{\text{max}}$  (Nujol mull) 3420m, 3360s, 3210s, 3290s, 3160 m(N–H str.), 2200s (CN str.), 1650s (C=N str.), 1590s (N–H bend), 1550s, 1365s, 1260s, 1210s, 1060s, 960s, 920m, 830s, 770m  $\text{cm}^{-1}$ .

### 5-Amino-1-(4-methoxyphenyl)-4-cyanoformimidoylimidazole **3b**

Recrystallisation of the product from diethyl ether gave pale green crystals of **3b** (0.62 g, 2.57 mmol, 62%). m.p. 165–168°C (decomp.);  $\delta_{\text{H}}$  (500 MHz,  $d_6$ -DMSO) 3.80 (s, 3H,  $\text{OCH}_3$ ), 6.10 (br. s, 2H,  $\text{NH}_2$ ), 6.95–7.09 (m, 4H, Ar–H), 7.14 (s, 1H, H-imidazole), 9.80 (br. s, 1H, NH) ppm:  $\nu_{\text{max}}$  (Nujol mull) 3320s, 3210s, 3190m, (N–H str.), 2220s, 2210s (CN str.), 1640s (C=N str.), 1570s (N–H bend), 1510s, 1450s, 1280s, 860s, 815m, 820m  $\text{cm}^{-1}$ .

### 5-Amino-1-(3,4-dimethylphenyl)-4-cyanoformimidoylimidazole **3c**

Recrystallisation of the product from diethyl ether gave pale yellow crystals of **3c** (0.82 g, 3.29 mmol, 8). m.p. 174–176°C (decomp.);  $\delta_{\text{H}}$

(500 MHz,  $d_6$ -DMSO) 2.30 (s, 6H,  $2 \times \text{CH}_3$ ), 6.07 (br. s, 2H,  $\text{NH}_2$ ), 7.14 (d, 1H, H-Ar), 7.21 (d, 1H, H-Ar), 7.30 (d, 1H, H-Ar), 7.33 (s, 1H, H-imidazole), 8.45 (br. s, 1H, NH);  $\nu_{\text{max}}$  (Nujol mull) 3320s, 3190s (N-H str.), 3040m, 2920m, 2200s (CN str.), 1640s (C=N str.), 1610s (N-H bend), 1440w, 870s, 820m  $\text{cm}^{-1}$ .

### General Procedure for the Preparation of 5-Amino-4-cyanoimidazoles 4a-c

A suspension of the corresponding 5-amino-4-cyanoformimidoylimidazole **3a-c**<sup>7-9</sup> (1.00 g) in potassium hydroxide solution (1M, 10  $\text{cm}^3$ ) was stirred at r.t. until TLC showed complete consumption of the starting material. The precipitated product was filtered, washed with water (8–10  $\text{cm}^3$ ), followed by a mixture of dry diethyl ether/ethanol (10:1), and air-dried in the absence of light to give the desired products **4a-c**.

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

Recrystallisation of the product from dry diethyl ether/ethanol (1:1) and air dried in the absence of light gave white crystals of **4a** (0.71 g, 3.01 mmol, 80%). m.p. 112–114°C (decomp.);  $\delta_{\text{H}}$  (500 MHz,  $d_6$ -DMSO) 5.40 (s, 2H,  $\text{CH}_2$ ), 6.60 (s, 2H,  $\text{NH}_2$ ), 7.01 (dd, 1H, Ar-H), 7.42 (s, 1H, H-imidazole), 7.63–7.68 (m, 2H, Ar-H), 7.85 (dd, 1H, Ar-H) ppm:  $\nu_{\text{max}}$  (Nujol mull) 3400m, 3370s, 3310s, 3210s, (N-H str.), 2220s (CN str.), 1650s (C=N str.), 1570s (N-H bend), 1520s, 1475s, 1430s, 1365s, 1280s, 1200s, 1060s, 1065s, 980s, 860m, 820m, 780s, 730m, 700m  $\text{cm}^{-1}$ .

#### 5-Amino-1-(4-methoxyphenyl)-4-cyanoimidazole 4b

Recrystallisation of the product from ethanol/methanol (1:1) gave pale yellow crystals of **4b** (0.54 g, 2.5 mmol, 61%). m.p. 171–172.5°C (decomp.);  $\delta_{\text{H}}$  (500 MHz,  $d_6$ -DMSO) 3.40(s, 3H,  $\text{OCH}_3$ ), 5.71 (s, 2H,  $\text{NH}_2$ ), 6.32 (dd, 2H, (Ar-H), 6.80 (dd, 2H, (Ar-H), 7.14 (s, 1H, H-imidazole) ppm:  $\nu_{\text{max}}$  (Nujol mull) 3390s, 3210s, 3160s, 3100w (N-H str.), 2220s, 2210s (CN str.), 1650s (C=N str.), 1610s (N-H bend), 1570s, 1520s, 1260s, 1160s, 1145s, 1020s, 865s, 815m, 770s, 735m  $\text{cm}^{-1}$ .

#### 5-Amino-1-(3,4-dimethylphenyl)-4-cyanoimidazole 4c

Recrystallisation of the product from ethanol/methanol (1:1) gave pale yellow crystals of **3c** (0.72 g, 3.39 mmol, 84%). m.p. 214–215°C (decomp.);  $\delta_{\text{H}}$  (500 MHz,  $d_6$ -DMSO) 2.27 (s, 6H,  $2 \times 4 \text{ CH}_3$ ), 6.07 (s, 2H,  $\text{NH}_2$ ), 7.2–7.14 (m, 3H, Ar-H), 7.20 (s, 1H, H-imidazole);  $\nu_{\text{max}}$  (Nujol mull) 3385s, 3350s, 3280s, 3100s (N-H str.), 2220s, 2200s (CN str.),

1660s (C=N str.), 1610s (N–H bend) and 1515w, 1255s, 1170s, 1155s, 1010s, 860s, 810m, 760s  $\text{cm}^{-1}$ .

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