A Facile Regioselective Synthesis of (5-Amino-4-cyano-1*H*-imidazol-1-yl) Benzoic Acids

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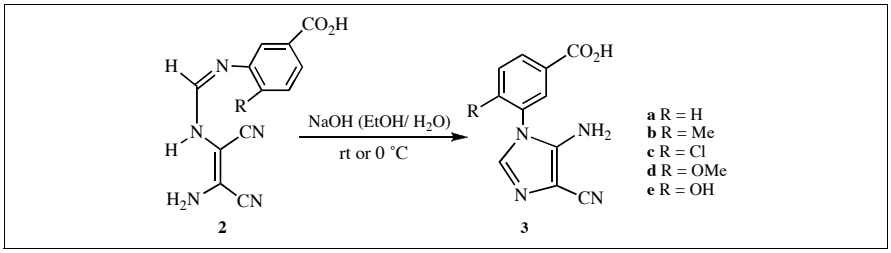

A simple and efficient method was developped for the synthesis of 3-(5-amino-4-cyano-1*H*-imidazol-1-yl)-4-substituted benzoic acids **3**. These compounds were isolated by intramolecular cyclisation of the corresponding 3-{[(*Z*)-2-amino-1,2-dicyano-vinyl]amino}methyleneaminobenzoic acids in the presence of base.

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INTRODUCTION.

The imidazole nucleus is present in a number of naturally occurring products and plays an important role in several biologically active heterocyclic structures. Compounds incorporating this ring are used as antihypertensive, antibacterial and anticancer drugs. They also found application in the agrochemical industry as herbicides and fungicides [1].

Imidazole and its derivatives have been investigated in dye chemistry, for both diazo precursor [2,3] and as coupling component [4]. The capacity of 2-amino-4,5-dicyanoimidazole to yield brilliant red disperse dyes of high fastness has been exploited commercially [5], and yellow dyes, prepared by condensation of 2-hydrazino-benzimidazole with indol-2,3-dione and subsequent alkylation, have been reported [6].

Despite their broad interest, few synthetic methods have been developed for the preparation of highly funtionalized 1-arylimidazoles [7,8]. A more recent publication refers to the synthesis of 4-acetylamino-3-(imidazol-1-yl) benzoic acid from 4-acetylamino-3-nitrobenzoic acid in a five step sequence. These compounds are moderate inhibitors of influenza virus sialidase, and the level of activity seen is largely independent of the substituent at the 4-position of the imidazole [9]. Recent research on the structural modification of 1-(4-benzoylphenyl)imidazole, a novel 20-HETE synthase inhibitor, indicates that introduction of a side chain with a carboxylic acid in the 4-position of the terminal aromatic ring results in increased ability to inhibit human renal microsomal production of 20-HETE [10].

As part of our interest in the synthesis of nitrogen heterocycles incorporating a benzoic acid unit [11,12], the present work describes an efficient and regioselective synthesis of functionalized imidazole derivatives **3**, **6** and **8** by intramolecular cyclisation of the corresponding amidines (**2** and **5**) in the presence of base.

Considering our previous work with reactive *azo* dyes for wool and polyamide fibres [13,14], we decided to investigate the possibility of using them as diazo components for coupling to 3-acylamino-*N,N*-dialkyl-anilides in the preparation of carboxylic reactive dyes.

RESULTS AND DISCUSSION.

The synthesis of amidines from the reaction of imidate **1** with amines has been extensively studied and always required the use of mild acid catalysis. Benzylamines [15], substituted anilines [16], alkylamines [17], cyclo-alkylamines [18], and ammonia [19] have been used in this reaction, which occurs under mild experimental conditions, in the presence of a catalytic amount of anilinium chloride.

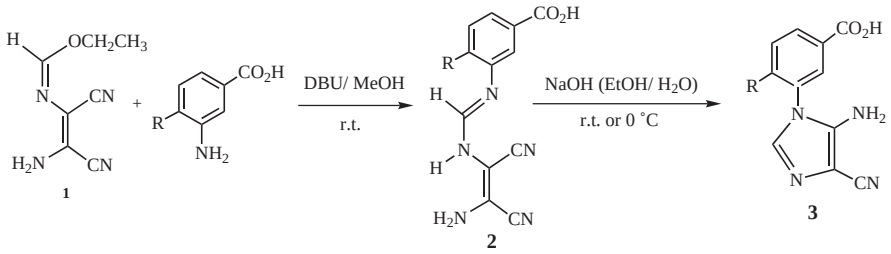
In the present work, amidines **2a-e** were prepared according to the procedure described for the reaction of imidate **1** with substituted anilines, but in this case, acid catalysis had to be replaced by the use of base. Addition of a catalytic amount of DBU overcomes the acidity of the aminobenzoic acid, probably increasing the nucleophilicity of the reacting nitrogen.

Treatment of formimidate **1** obtained from diamino-maleonitrile and triethyl orthoformate [20], with an equimolar amount of the appropriate aromatic amine at room temperature in methanol in the presence of a

catalytic amount of DBU, generated the corresponding formamidines **2a-e** as solid materials in yields ranging from 32-81% (Scheme 1, Table 1). In all cases, isolation was achieved by simple filtration of the product and no further purification was required.

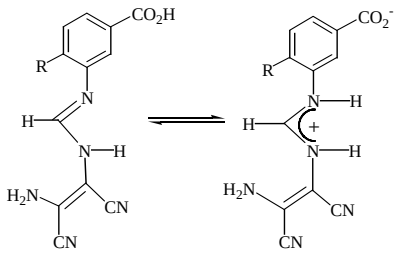
These compounds were characterised by ir and nmr spectroscopy. The presence of the carbonyl group is confirmed by ir, which shows a medium/strong band in the 1701-1677 cm^{-1} region. In the ^{13}C nmr spectrum, signals at δ 167-168 ppm were assigned to this functional group. The cyano group could be identified by the signals in the IR spectrum (two bands in the 2227-2233 cm^{-1} and 2194-2210 cm^{-1} region) and also in the ^{13}C nmr (δ 113.5-114.6 ppm and 114.9-115.9 ppm). The ^1H nmr spectrum of compounds **2a** and **2d** shows two sets of resonances for the aromatic protons. The remaining signals are broad singlets, also suggesting the presence of an intramolecular acid-base equilibrium, as is represented in Scheme 2.

Scheme 1



2, 3 a R = H, **b** R = Me, **c** R = Cl, **d** R = OMe, **e** R = OH

Scheme 2

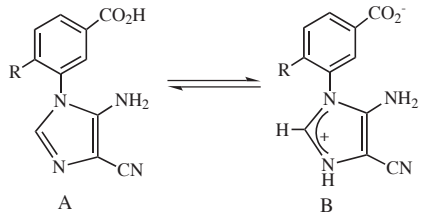


When the amidines (**2a-e**) were added to a saturated solution of NaOH in ethanol/water at room temperature, good yields (77-100%) of the corresponding 3-(5-amino-4-cyano-1*H*-imidazol-1-yl) benzoic acids **3** were obtained (Scheme 1, Table 1). These compounds were fully characterised by high resolution mass spectrometry, ir and nmr (^1H and ^{13}C) spectroscopy.

In the ir spectra of compounds **3a**-**d**, a sharp signal was present between 2215 and 2169 cm^{-1} characteristic of the stretching vibration of the cyano group. A signal around δ 117 ppm in the ^{13}C nmr spectrum was also assigned to this functional group.

Two sets of signals were observed in the ^1H nmr (DMSO-d_6) spectrum for compounds **3b** and **3d**. This may be due to the presence, in the solution of isomers A and B (in a 70:30 ratio), as the chemical shift of the imidazole C-H changes from a sharp singlet in the δ 7.20-7.23 ppm region (assigned to isomer A) to a broad singlet around δ 7.60-7.90 ppm (assigned to isomer B).

Scheme 3



Isomer B must also predominate in the solid state. In the ir spectrum, the absorption band expected for the carboxylic acid in the 1700-1680 cm^{-1} region, is absent in most of the compounds.

In order to avoid subsequent problems associated with the intramolecular acid-base equilibrium, the carboxylic acid was protected as the ester group. When the corresponding aniline **4a** was reacted with imidate 1 (Scheme 4) in ethanol, in the presence of a catalytic amount of anilinium chloride and the solution was stirred at 0-5 ºC, the amidine **5a** precipitated from the reaction mixture and was isolated in 80% yield.

The reaction of imidate **1** and **4b** carried out in methanol at room temperature gave amidine **5b**, which precipitated from the reaction mixture and was filtered after 20 h (68% yield).

In the ir spectrum of these compounds, sharp bands are observed due to the NH_2 stretching vibration, in the range of 3456 - 3310 cm^{-1}; the CN groups were identified as two distinct bands between 2223 and 2202 cm^{-1} and the

C=O (ester) groups were confirmed by bands at 1711 and 1701 cm^{-1} for amidines **5a** and **5b**, respectively.

Their ^1H and ^{13}C nmr (DMSO-d6) spectra showed that only one isomer was present. In the ^1H nmr spectrum, a single set of signals could be assigned to the aromatic protons and to the ester groups. The same applies to the protons of the amino function [δ 6.45 (**5a**) and δ 6.60 (**5b**) ppm], C-H (δ 7.90-8.20 ppm) and N-H [δ 10.2 (**5a**) and δ 10.30 (**5b**) ppm]. The aromatic protons in compound **5b** do not exhibit a normal AA'BB' pattern, as would be expected for a *p*-substituted aromatic ring. The band corresponding to the protons in the *ortho* position is always broad and the same happens to the amidine C-H signal. This situation was previously reported for analogous *N*-aryl amidines [16]. A careful study on the possible causes of this band broadening suggests that prototropic tautomerism is not involved. The most likely explanation for the dynamic behaviour in solution is restricted rotation around the C_4-N_3 bond of the *E-syn* configuration (represented for comounds **5a,b** in Scheme 4) to give the *E-anti* configuration.

Table 1

Synthesis of Amidines (**2** and **5**) and Imidazoles (**3, 6** and **8**)

Compound	Time (h)	Yield (%)
2a	18	64
2b	24	70
2c	6	32
2d	48	42
2e	2	81
3a	2.5	77
3b	1	100
3c	2 [a]	99
3d	1.5	100
3e	2 [a]	99
5a	27 [a]	80
5b	20	68
6a	2 [a]	39
6b	16	24 [b]
8	[c]	85

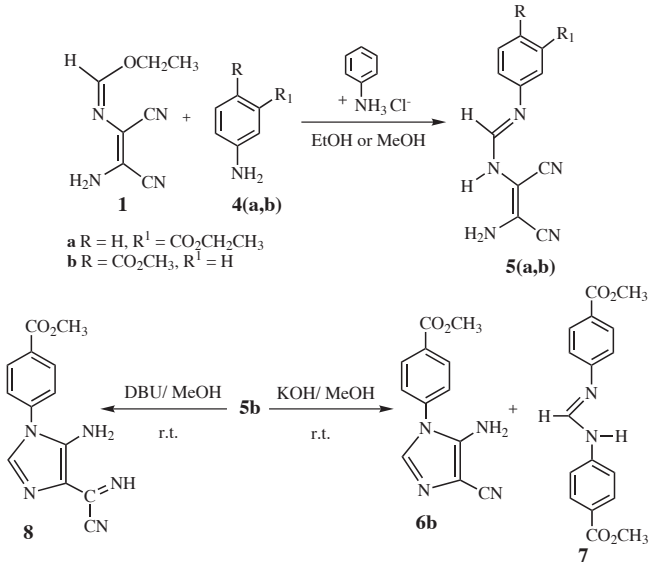
[a] Experiments carried out at 0 ºC; [b] Isolated in a mixture with compound **7** (73%); [c] Reaction time 5 minutes.

Cyclization of amidine **5a**, in an aqueous solution of potassium hydroxide, at low temperature (2h), gave the corresponding imidazole (**6a)** as a white solid, isolated in 39% yield. This compound was characterised by ir, ^1H and ^{13}C nmr spectroscopy and also by high mass resolution.

Attempts to cyclise amidine **5b** by the addition of a 4 *M* aqueous solution of potassium hydroxide (Method A) led to the isolation of a dimeric species identified as structure **7** by elemental analysis and spectroscopic data (Scheme 4). When a saturated solution of KOH in methanol was used and the amidine concentration was reduced (*ca*. half of the previous value) (Method B), a cream solid was isolated and proved to be a mixture of imidazole **6b** and the dimer **7** (40:60) on the basis of ^1H nmr spectroscopy.

The use of DBU as a base led to the formation of a white solid identified as imidazole **8** (85% yield).

Scheme 4



It is known that the diazotization of heterocyclic amines is sometimes difficult, particulary in the case of imidazole derivatives. To our knowledge, very little information on the synthesis and properties of dyes from imidazolyl diazo components has been published recently [21].

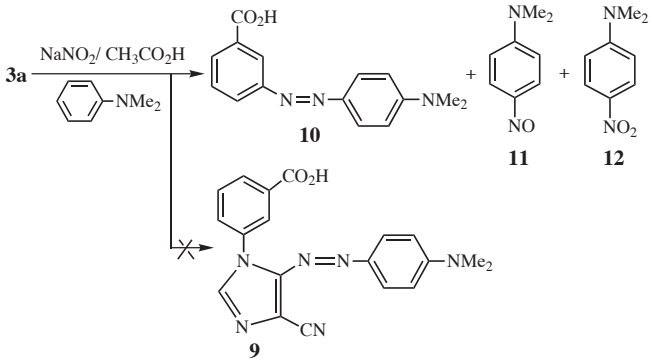
Considering that *azo* dyes, prepared from the carboxylic imidazoles synthesised in this work as diazo components and 3-acylamino-*N,N*-dialkylanilides as coupling components, were expected to present high tintorial strength good wash and light fastness on the dyeing of wool and polyamide fibres, several attemps were made to diazotise imidazole **3a** and react it with *N,N*-dialkylanilines to generate compounds of type **9** (Scheme 5).

The diazotization of **3a** was carried out with potassium or sodium nitrite in a strongly acidic medium (sulphuric acid - Method 1 and hydrochloric acid - Methods 2 and 3) always leading to extensive degradation of the reaction mixture.

When a low acidic medium was used (acetic acid, Method 4), compounds **10**, **11** and **12**, were isolated and identified by ir, ^1H and ^{13}C nmr spectroscopy, and also mass spectrometry (Scheme 5). Dye **10** was obtained as an orange solid in 7% yield, and the structure was assigned by comparison of its spectroscopic data with that of an authentic sample [13]. Nitroso and nitro-*N,N*-

dimethylamines **11** and **12** were also obtained as solid materials in 19 and 4% yields, respectively.

Scheme 5



These results indicate that the diazotization of the amino group of the imidazole does not occur under the experimental conditions that were used. Under strongly acidic conditions, the extensive protonation of the imidazole ring considerably reduces the nucleophilicity of the amine function, preventing the formation of the desired product.

Mild acidic conditions (acetic acid) led to the formation of a complex reaction mixture from which it was possible to isolate 3-[(*N,N*-dimethylaminophenyl)-4'-diazenyl]-benzoic acid (**10**, 7%), 4-nitroso-*N,N*-dimethylaniline (**11**, 19%) and 4-nitro-*N,N*-dimethylaniline (**12**, 4%).

A simple and efficient method was developed for the synthesis of 3-{[(*Z*)-2-amino-1,2-dicyanovinyl] methyleneaminobenzoic acids **2** and 3-(5-amino-4-cyano-1*H*-imidazol-1-yl) benzoic acids **3** incorporating a carboxylate function in the aromatic ring. Similar imidazoles with an ester function (**6a**,**b**) prepared from the corresponding amidine (**5a**,**b**) were also isolated.

The high isolated yields of compounds **3** make them valuable precursors of fused heterocyclic systems incorporating an imidazole nucleus substituted in the 1-position with a carboxylic acid or derivative. These compounds would be able to interact with biomolecules through strong H-bonding or covalent linkages. To our knowledge, their synthesis was never reported by previous methods.

EXPERIMENTAL

All melting points were measured on a Gallenkamp apparatus and are uncorrected. The ir spectra were determined on a Perkin Elmer FTIR-1600 using KBr discs or nujol emulsions between NaCl plates. nmr Spectra were run at 25 ºC. ^{1}H nmr spectra were recorded at 300 MHz and ^{13}C nmr spectra were determined at 75.4 MHz both on a Varian Unity Plus Spectrometer. Low resolution EI and CI mass spectra were determined on a Unicam GC-MS 120. High resolution mass spectra were performed at the "Unidad de Espectrometria de Masas" of the University of Vigo, Spain. Elemental analyses were carried out on a Leco CHNS 932 instrument. TLC was carried out on plates coated with 0.25 mm thick silica gel 60 F_{254}. Column chromatography was performed on silica gel (<230 mesh) under conditions that are described below. Light petroleum refers to the fraction boiling in the range 40-60 °C. Ethyl-3-aminobenzoate and methyl-4-aminobenzoate were prepared according to a standard procedure [22]. Ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl) formimidate was synthesised using a procedure described in the literature [20].

General Procedures for the Preparation of the 3-{[(*Z*)-2-Amino-1,2-dicyanovinyl]amino}methyleneaminobenzoic acids 2. 2-Amino-1,2-dicyanovinylformimidate (1.0 g, 6.1 mmol) and DBU (0.093 mL, 0.61 mmol) were added to a suspension of the aromatic amine (6.1 mmol) in methanol (8 mL), with efficient stirring. The mixture was kept stirring at room temperature until TLC (chloroform–ethanol 8:2) showed that all the formimidate (**1**) had been consumed (Table 1). Diethyl ether was added and the precipitate was collected by filtration, washed with the same solvent or methanol (compound **2a**) and dried under vacuum (25 ºC) in the dark to give the required product.

3-{[(*Z*)-2-Amino-1,2-dicyanovinyl]amino}methyleneaminobenzoic acid (2a). Reaction of **1** with 3-aminobenzoic acid gave the amidine **2a** as an off-white solid, 0.10 g (64%), mp 276.9-278.0 ºC; R_f 0.22 (chloroform–ethanol 8:2). ir (KBr 1%): 3448, 3334, 2901, 2690, 2566, 2233 (CN), 2194 (CN), 1699 (CO), 1646, 1596, 1556, 1461 cm^{-1}. ^{1}H nmr (acetone- d_6/ DMSO-d_6 50:3) isomers A and B in 70:30 ratio : δ 6.10 (s, 2 H, NH_2 A and B), 7.45 (t, 5-H B, 1 H, J = 8.0 Hz), 7.47 (t, 1 H, 5-H A, J = 8.0 Hz), 7.68-7.75 (m, 1 H, 6-H A and B), 7.95 (br s, 1 H, 2-H A and B), 8.15 (br s, 1 H, CH A and B), 8.30 (br s, 1 H, 4-H A and B), 10.0 ppm (br s, 1 H, NH A and B). ^{13}C nmr (acetone-d_6/ DMSO-d_6 50:3): δ 107.0 (C-2), 114.6 (CN), 115.9 (CN), 120.2 (C-3), 124.7 (Ar), 124.0 (br, Ar), 129.8 (Ar), 130.1 (Ar), 132.8 (Ar), 140.6 (Ar), 148.4 (HC=N), 167.8 (CO) ppm. ms (EI): *m/z* (%) 256 (M^+ +1, 3), 255 (M^+, 13).

3-{[(*Z*)-2-Amino-1,2-dicyanovinyl]amino}methyleneamino-4-methylbenzoic acid (2b). Reaction of **1** with 3-amino-4-methylbenzoic acid gave the amidine **2b** as an off-white solid, 1.15 g (70%), mp above 300 ºC; R_f 0.48 (chloroform–ethanol 8:2). ir (KBr 1%): 3458, 3341, 3150, 2980, 2551, 2229 (CN), 2207 (CN), 1685 (CO), 1639, 1609, 1584, 1557, 1458 cm^{-1}. ^{1}H nmr (acetone-d_6/ DMSO-d_6 50:3): δ 2.43 (s, 3 H, CH_3), 5.90 (br s, 2 H, NH_2), 7.36 (d, 1 H, 5-H, J = 8.0 Hz), 7.69 (dd, 1 H, 6-H, J = 8.0 and 1.50 Hz), 8.14 (s, 1 H, CH), 8.60-8.90 (br s, 1 H, 2-H), 9.00-9.30 (br s, 1 H, NH) ppm. ^{13}C nmr (acetone-d_6/ DMSO-d_6 50:3): δ 18.2 (CH_3), 107.0 (C-2), 114.5 (CN), 115.9 (CN), 120.0 (C-1), 122.0 (br, Ar), 125.6 (Ar), 130.3 (Ar), 131.3 (Ar), 134.1 (Ar), 140.0 (Ar), 149.2 (HC=N), 168.0 (CO) ppm. ms (EI): *m/z* (%) 270 (M^+ +1, 5), 269 (M^+, 31).

3-{[(*Z*)-2-Amino-1,2-dicyanovinyl]amino}methyleneamino-4-chlorobenzoic acid (2c). Reaction of **1** with 3-amino-4-chlorobenzoic acid gave the amidine **2c** as a pinkish solid, 0.56 g (32%), it did not melt until 300 ºC; R_f 0.37 (chloroform–ethanol 8:2); ir (KBr 1%): ν 3462, 3312, 2233 (CN), 2208 (CN), 1699 (CO), 1639, 1589, 1542, 1439 cm^{-1}. ^{1}H nmr (acetone-d_6/ DMSO-d_6 50:3): δ 6.18 (br s, 2 H, NH_2), 7.62 (d, 1 H, 5-H, J = 8.1 Hz), 7.72 (dd, 1 H, 6-H, J = 8.1 and 1.80

Hz), 8.22 (s, 1 H, CH), 9.20 (br s, 1 H, 2-H) ppm. NH was not shown on the spectrum. ^{13}C nmr (acetone-d_6/ DMSO-d_6 50:3): δ 106.0 (C-2), 114.3 (CN), 115.6 (CN), 121.2 (C-1), 121.9 (Ar), 125.6 (Ar), 127.7 (Ar), 130.3 (Ar), 131.4 (Ar), 136.8 (Ar), 148.5 (HC=N), 167.4 (CO) ppm.

3-{[(*Z*)-2-Amino-1,2-dicyanovinyl]amino}methyleneamino-4-methoxybenzoic acid (2d). Reaction of **1** with 3-amino-4-methoxybenzoic acid gave the amidine **2d** as a pinkish solid, 0.73 g (42%), mp 243.1-245.7 ºC; R_f 0.60 (chloroform–ethanol 8:2). ir (KBr 1%): ν 3460, 3314, 2942, 2227 (CN), 2205 (CN), 1701 (CO), 1639, 1600, 1545, 1490, 1446 cm^{-1}. ^{1}H nmr (acetone-d_6/ DMSO-d_6 50:3) isomers A and B in 70:30 ratio: δ 3.97 (s, 3 H, OCH_3 B), 4.04 (s, 3 H, OCH_3 A), 6.0 (s, 2 H, NH_2 A and B), 7.11 (d,1 H, 5-H B, J = 8.4 Hz), 7.16 (d,1 H, 5-H A, J = 8.4 Hz), 7.73 (dd,1 H, 6-H B, J = 8.4 and 2.0 Hz), 7.76 (dd, 1 H, 6-H A, J = 8.4 and 2.0 Hz), 8.20 (br s, 1 H, CH, A and B), 9.20 (br s, 1 H, 2-H A and B) ppm. NH was not showed on the spectrum. ^{13}C nmr (acetone-d_6/ DMSO-d_6 50:3): δ 55.7 (OCH_3), 106.0 (C-2), 109.1 (Ar), 109.9 (Ar), 113.5 (CN), 114.9 (CN), 123.2 (Ar), 125.4 (Ar), 147.5 (HC=N), 151.9 (Ar), 167.0 (CO) ppm. The assignments were supported by the Dept 45 technique. ms (EI): *m/z* (%) 285 (M^+, 8).

3-{[(*Z*)-2-Amino-1,2-dicyanovinyl]amino}methyleneamino-4-hydroxybenzoic acid (2e). Reaction of **1** with 3-amino-4-hydroxybenzoic acid gave the amidine **2e** as a pink solid, 1.34 g (81%), it did not melt until 313 ºC; R_f 0.45 (chloroform–ethanol 8:2). ir (KBr 1%): ν 3334, 2233 (CN), 2210 (CN), 1677 (CO), 1637, 1602, 1550, 1458 cm^{-1}. ^{1}H nmr (acetone- d6/ DMSO-d_6 50:3) δ 7.02 (d, 1 H, 5-H, J = 8.1 Hz), 7.63 (dd, 1 H, 6-H, J = 8.1 and 2.1 Hz), 8.24 (br s, 1 H, CH), 8.90-9.40 (br s, <2H, 2-H) ppm. NH_2 and NH were not shown on the spectrum. ^{13}C nmr (acetone-d_6/ DMSO-d_6 50:3): δ 109.1 (Ar), 109.9 (Ar), 114.9 (CN), 113.5 (CN), 123.2 (Ar), 125.4 (Ar), 151.9 (Ar), 147.5 (HC=N), 167.0 (CO) ppm.

Ethyl 3-{[(*Z*)-2-amino-1,2-dicyanovinyl]amino}methyleneaminobenzoate (5a). Ethyl 3-aminobenzoate (1.0 g, 6.06 mmol) and anilinium chloride (catalytic amount) were added to a suspension of 2-amino-1,2-dicyanovinylformimidate (**1**) (1.0 g, 6.1 mmol) in ethanol (7 mL) while the mixture was stirred in an ice bath (0-5 ºC). The mixture was kept stirring at low temperature for 27 hours. The reaction was monitored by TLC (chloroform–ethanol 9:1). The precipitate was collected by filtration, washed with diethyl ether and dried under vacuum (25 ºC) in the dark to give amidine **5a** as an off-white solid, 1.38 g (80%); R_f 0.54 (chloroform–ethanol 9:1). ir (KBr 1%): ν 3449, 3332, 2222, 2202, 1711, 1639, 1611, 1560, 1492 cm^{-1}. ^{1}H nmr (DMSO-d6): δ 1.3 (t, 3 H, CH_3, J = 7.3 Hz), 4.32 (q, 2 H, CH_2, J = 7.3 Hz), 6.45 (s, 2 H, NH_2), 7.48 (t, 1 H, 5-H, J = 7.5 Hz), 7.62 (d, 1 H, 4-H or 6-H, J = 7.5 Hz), 7.90-8.20 (m, 3 H, C-H, 2-H and 6-H or 2-H and 4-H), 10.20 (br d, 1 H, *J* = 4.4 Hz, N-H) ppm. ms (EI): *m/z* (%) 283 (M^+, 49).

Methyl 4-{[(*Z*)-2-amino-1,2-dicyanovinyl]amino}methyleneaminobenzoate (5b). 2-Amino-1,2-dicyanovinylformimidate **1** (1.01 g, 6.16 mmol) was added to a suspension of 4-methylaminobenzoate (0.93 g, 6.16 mmol) in methanol (10 ml). A catalytic amount of anilinium chloride was added to the reaction mixture that was stirred at 23 ºC for 20 hours. The solid suspension was filtered and washed with methanol leading to a lemon-yellow solid identified as compound **5b**, 1.12 g (68%), mp 180.0-181.0 ºC (dec). ir (oil): ν 3456, 3310, 2223, 2203, 1701, 1644, 1603, 1583 cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 3.80 (s, 3 H, OCH_3), 6.60 (s, 2 H, NH_2), 7.70 (br s, 2 H, 3-H and 5-H), 7.90 (d, 2 H, 2-H and 6-H, J = 9.0 Hz), 8.00 (br s, 1 H, CH), 10.30 (s, 1 H, NH) ppm. ^{13}C nmr (DMSO-d_6): δ 51.8 (OCH_3), 104.2 (C-2), 114.7 (CN), 115.5 (CN), 117.7 (Ar), 120.1 (C-1), 123.3 (Ar), 130.6 (Ar), 143.6 (Ar), 147.1 (HC=N), 168.8 (CO) ppm. ms (CI CH_4): *m/z* (%) 270 (M^++1, 20), 269 (M^+, 42). *Anal*. Calcd for $C_{13}H_{11}N_5O_2$: C, 58.0; H, 4.10; N, 26.0. Found: C, 57.88; H, 4.33; N, 25.66.

The mother liquor was concentrated in the rotary evaporator (bath temperature 35 ºC) leading to a yellow solid, which was collected by filtration and washed with dichloromethane. The product was identified as diaminomaleonitrile, 0.21 g (32%) by comparison of its IR spectrum with that of an authentic sample [23a].

General Procedure for Preparation of the 3-(5-Amino-4-cyano-1*H*-imidazol-1-yl) benzoic acids 3. Formamidine (**2**) (5.85 mmol) was added to a saturated solution of sodium hydroxide in ethanol/water 1:0.01 (38.9 mL) and the mixture was stirred at room temperature for 1-2.5 hours (Scheme 1). The reaction was monitored by TLC (chloroform–ethanol 7.5:2.5). Diethyl ether was added and the precipitate was collected by filtration, washed with the same solvent and dried under vacuum (25 ºC) to give the required imidazole **3**.

3-(5-Amino-4-cyano-1*H*-imidazol-1-yl) benzoic acid (3a). The product of cyclisation of **2a** was obtained as a brown solid, 1.33 g (77 %), mp above 322 ºC; R_f 0.61 (chloroform–ethanol 2.5:7.5). ir (KBr 1%): ν 3407, 2212, 1678, 1654, 1560, 1519 cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 6.10 (br s, 2 H, NH_2), 7.32-7.36 (m, 1 H, 6 or 4-H), 7.37 (s, 1 H, C-H), 7.44 (t, 1 H, 5-H, J = 7.5 Hz), 7.81 (t, 1 H, 2-H, J = 1.8 Hz), 7.90-7.96 (m, 1 H, 4 or 6-H). ^{13}C nmr (DMSO-d_6): δ 90.0 (C-4), 117.2 (CN), 125.4 (Ar), 125.6 (Ar), 128.6 (Ar), 129.2 (Ar), 132.6 (C-2), 133.0 (Ar), 142.8 (Ar), 147.4 (C-5), 168.0 (CO). hrms: calcd. for $C_{11}H_8N_4O_2$ [M^+] 228.0647; found 228.0646.

3-(5-Amino-4-cyano-1*H*-imidazol-1-yl)-4-methylbenzoic acid (3b). The product of cyclisation of **3b** was obtained as an off-white solid 1.42 g (100%), mp above 322 ºC; R_f 0.56 (chloroform–ethanol 2.5:7.5). ir (KBr 1%): ν 3309, 3178, 2209, 1654, 1599, 1578, 1552, 1516, 1451 cm^{-1}. ^{1}H nmr (DMSO-d_6) isomers A and B in 70:30 ratio: δ 2.04 (s, 3 H, CH_3 A), 2.25 (s, 3 H, CH_3 B) 6.0 (br s, 2 H, NH_2 A and B), 7.05 (d, 1 H, 5-H B, J = 8.0 Hz), 7.23 (s, 1 H, C-H, A), 7.32 (d, 1 H, 5-H A, J = 8.0 Hz), 7.48 (dd, 1 H, 6-H B, J = 8.0 Hz and 1.5 Hz), 7.65 (d, 1 H, 2-H A, J = 1.5 Hz), 7.60-7.90 (br s, 1 H, C-H B), 7.89 (dd, 1 H, 6-H A, J = 8.0 Hz and 1.5 Hz), 7.94 (d, 1 H, 2-H B, J = 1.5 Hz,) ppm. ^{13}C nmr (DMSO-d6): δ 18.2 (OCH_3), 98.8 (C-4), 117.0 (CN), 128.3 (Ar), 129.9 (Ar), 130.2 (Ar), 131.3 (Ar), 132.5 (C-2), 135.2 (Ar), 141.1 (Ar), 147.9 (C-5), 167.2 (CO) ppm. hrms: calcd. for $C_{12}H_{10}N_4O_2$ [M^+] 242.0804; found 242.0808.

3-(5-Amino-4-cyano-1*H*-imidazol-1-yl)-4-chlorobenzoic acid (3c). The product of cyclisation of **2c** was obtained as a pinkish solid, (1.54 g, 99%), mp above 320 ºC, R_f 0.59 (chloroform–ethanol 2.5:7.5). ir (KBr 1%): ν 3396, 2215, 1647, 1611, 1589, 1560, 1516, 1417 cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 6.18 (br s, 2 H, NH_2), 7.29 (s, 1 H, C-H), 7.58 (d, 1 H, 5-H, J = 8.4 Hz,), 7.81 (d, 1 H, 2-H, J = 1.8 Hz), 7.97 (dd, 1 H, 6-H, J = 8.4 and 1.8 Hz) ppm. ^{13}C nmr (DMSO-d_6): δ 89.5 (C-4), 117.2 (CN), 129.1 (Ar), 129.8 (Ar), 130.2 (Ar), 131.3 (Ar), 132.3 (Ar), 132.3 (C-2), 141.8 (Ar), 148.2 (C-5), 166.6 (CO) ppm. hrms: calcd. for $C_{11}H_7N_4O_2{}^{35}Cl$ [M^+] 262.0258; found 262.0261, calcd. for $C_{11}H_7N_4O_2{}^{37}Cl$ [M^+] 264.0228; found 264.0234.

3-(5-Amino-4-cyano-1*H*-imidazol-1-yl)-4-methoxybenzoic acid (3d). The product of cyclisation of **2d** was obtained as a pinkish solid 1.51 g (100%), mp above 320 ºC; R_f 0.39 (chloroform–ethanol 2.5:7.5). ir (KBr 1%): ν 3326, 3144, 2842, 2199, 1654, 1610, 1544 cm^{-1}. ^1H nmr (DMSO- d_6) isomers A and B in 80:20 ratio: δ 3.73 (s, 3 H, OCH_3 B), 3.79 (s, 3 H, OCH_3 A), 5.90 (br s, 2 H, NH_2), 6.68 (d, 1 H, 5-H B, J = 8.1 Hz), 7.12 (d, 1 H, 5-H A, J = 8.1 Hz), 7.20 (s, 1 H, C-H, A), 7.23 (s, 1 H, 2-H A), 7.53 (br d, 1 H, 6-H B, J = 8.1Hz), 7.68 (d, 1 H, 2-H B, J = 1.8 Hz), 7.80-7.90 (br s, 1 H, C-H B), 7.97 (dd, 1 H, 6-H A, J = 8.1 Hz and 1.8 Hz) ppm. ^{13}C nmr (DMSO-d_6): δ 55.9 (OCH_3), 89.8 (C-4), 114.4 (Ar), 117.5 (CN), 120.5 (Ar), 129.2 (Ar), 131.7 (Ar), 133.0 (C-2), 133.4 (Ar), 148.3 (C-5), 155.0 (Ar), 168.6 (CO) ppm. hrms: calcd. for $C_{12}H_{10}N_4O_3$ [M^+] 258.0753; found 258.0750.

3-(5-Amino-4-cyano-1*H*-imidazol-1-yl)-4-hydroxybenzoic acid (3e). The product of cyclisation of **2e** was obtained as a brown solid (1.41 g, 99 %), mp above 320 ºC; R_f 0.47 (chloroform–ethanol 2.5:7.5). ir (KBr 1%): ν 3415, 2211, 2200, 1648, 1629, 1603, 1572, 1522 cm^{-1}. ^1H nmr (DMSO-d_6): δ 6.19 (d, 1 H, 5-H, J = 9.0 Hz), 6.63 (br s, 2 H, NH_2), 7.16 (s, 1H, C-H), 7.45-7.51 (m, 2 H, 2 and 6-H) ppm. ^{13}C nmr (DMSO-d_6): δ 90.7 (C-4), 118.2 (CN), 119.9 (Ar), 120.2 (Ar), 123.7 (Ar), 126.6 (Ar), 130.6 (Ar), 132.1 (C-2), 150.0 (C-5), 165.5 (Ar), 171.8 (CO) ppm. hrms: calcd. for $C_{11}H_8N_4O_3$ [M^+] , 244.0596; found 244.0597.

Ethyl 3-(5-amino-4-cyano-1*H*-imidazol-1-yl) benzoate (6a). An aqueous solution of potassium hydroxide 2 *M* (0.5 mL) was added to a suspension of formamidine **5a** (0.14 g; 0.50 mmol) in ethanol (2 mL), and the mixture was stirred in an ice bath (0-5 ºC) for 2 hours. The precipitate was collected by filtration and washed with cold water, ethanol and diethyl ether, and after drying under vacuum (30 ºC) imidazole **6a** was obtained as an white solid, (0.05 g, 39%), mp 204.1-206.0 ºC. ir (KBr 1%): ν 3358, 3198, 2210, 1720, 1654, 1608, 1579, 1521, 1456 cm^{-1}. ^1H nmr (DMSO-d_6): δ 1.32 (t, 3 H, CH_3, J = 7.2 Hz), 4.34 (q, 2 H, CH_2, J = 7.2 Hz), 6.23 (br s, < 2 H, NH_2), 7.46 (s, 1 H, CH), 7.66-7.80 (m, 2 H, 5-H and 6-H), 7.95 (t, 1 H, 2-H, J = 1.8 Hz,), 8.05 (d, 1 H, 4-H, J = 7.2 and 1.8 Hz) ppm. ^{13}C nmr (DMSO-d_6): δ 14.1 (CH_3), 61.2 (CH_2), 91.0 (C-4), 117.0 (CN), 126.0 (Ar), 129.3 (Ar), 130.3 (Ar), 130.5 (Ar), 132.6 (Ar, C-2), 134.3 (Ar), 147.5 (C-5), 164.9 (CO). The assignments were supported by HMBC, HMQC and Dept techniques. hrms: calcd. for $C_{13}H_{12}N_4O_2$ [M^+] , 256.0960; found 256.0969.

Attemps to Prepare Methyl 4-(5-amino-4-cyano-1*H*-imidazol-1-yl) benzoate (6b). ***Method A.*** An aqueous solution of KOH 4 *M* (2 mL) was added to a suspension of formamidine **5b** (0.166 g, 0.62 mmol) in ethanol (1 mL), kept in an ice bath with efficient stirring. A yellow colour immediately developed in solution and the solid was stirred at 23 ºC for 17 hours. The suspension was filtered and washed with water to give a cream solid identified as methyl 4-{[4-(methoxycarbonyl)phenyl]-amino}methyleneaminobenzoate (**7**), 0.06 g (61%), mp 186-188 ºC (dec). ir (oil): ν 3428, 1716, 1708, 1654, 1628, 1593, 1573 cm^{-1}. ^1H nmr (acetone-d_6/DMSO-d_6 5:4): δ 3.90 (s, 6 H, 2xCH_3), 7.20 (br s, 4 H, 3-H and 5-H), 7.90 (d, 4 H, 2-H and 6-H, J = 9.1 Hz), 8.40 (br s, 1 H, CH), 10.10-10.30 (br s, 1 H, NH) ppm. ^{13}C nmr (acetone-d_6: DMSO-d_6 5:4): δ 51.8 (CH_3), 118.9 (C-3 and C-5), 124.3 (C-1), 130.9 (C-2 and C-6), 149.1 (C-H), 166.5 (CO) ppm. ms (CI CH_4): *m/z* (%) 313 (M^++1, 20), 312 (M^+, 100). *Anal.* Calcd for $C_{17}H_{161}N_2O_4$: C, 65.40; H, 5.10; N, 9.00. Found: C, 65.30; H, 5.30; N, 9.10.

Method B. A saturated solution of KOH in methanol (5 mL) was added to a suspension of formamidine **5b** (0.385 g, 1.4 mmol) in methanol (2 mL) and the mixture was stirred at 22 ºC for 16 hours. The solid was collected by filtration and washed with methanol. The cream solid (0.21 g) was a mixture of imidazole **6b** and dimer **6** in a 1:1.5 ratio 24%: 73%), as evidenced by ^1H nmr on the crude solid.

The signals for the dimer **7** were identified in the ^1H and ^{13}C nmr spectra, enabling the assignment of the bands for the imidazole **6b**. ^1H nmr (acetone-d_6/ DMSO-d_6 6.0:2.5): δ 3.90 (s, 3 H, OCH_3), 6.10 (br s, 2 H, NH_2), 7.40 (s, 1 H, CH), 7.70 (d, 2 H, 3-H and 5-H, J = 9.0 Hz), 8.20 (d, 2 H, 2-H and 6-H, J = 9.0 Hz) ppm. ^{13}C nmr (acetone-d_6: DMSO-d_6 6:2.5): δ 52.6 (OCH_3), 93.0 (C-4), 117.1 (CN), 125.8 (Ar), 131.1 (Ar), 131.5 (C-2), 132.6 (Ar), 138.8 (Ar), 147.6 (C-5), 166.1 (*C*O) ppm.

Methyl 4-{5-amino-4-[cyano(imino)methyl]-1*H*-imidazol-1-yl}benzoate 8. DBU (0.30 mL, 2.01 mmol) was added to a suspension of formamidine **5b** (0.22 g, 0.81 mmol) in methanol (5 mL), with efficient stirring. The mixture was stirred at 22 ºC and 5 minutes later the white solid suspension was collected by filtration and washed with methanol. The solid was identified as compound **8**, 0.185 g (85%), mp 176-177 ºC. ir (oil): ν 3389, 3274, 3118, 1924, 1716, 1615, 1590 cm^{-1}. ^1H nmr (DMSO-d_6): δ 3.90 (s, 3 H, OCH_3), 6.80 (br s, 2 H, NH_2), 7.60 (s, 1 H, CH), 7.70 (d, 2 H, 3-H and 5-H, J = 8.8 Hz), 8.10 (d, 2 H, 2-H and 6-H, J = 8.8 Hz), 11.20 (br s, 1 H, NH) ppm. ^{13}C nmr (DMSO-d_6): δ 52.5 (OCH_3), 113.2 (CN), 116.6 (C-4), 124.7 (Ar), 129.2 (Ar), 130.8 (Ar), 131.8 (C-2), 137.9 (Ar), 142.9 (C=NH), 143.6 (C-5), 165.5 (*C*O) ppm. ms (EI): *m/z* (%) 270 (M^+ +1, 9), 269 (M^+, 38).

Attemps to Prepare 3-(4-Cyano-5-{[4-(dimethylamino)-phenyl]-diazenyl}-*1H*-imidazol-1-yl)benzoic acid (9). ***Method 1.*** Sodium nitrite (0.008 g, 0.12 mmol) was added to concentrated H_2SO_4 (0.07 mL) with external cooling (0 ºC). The suspension was stirred for 10 minutes and a mixture of propionic-acetic acids 1:5 (0.012 mL) was added. Imidazole **3a** (0.027 g, 0.12 mmol) was added in portions and the mixture was left stirring for 30 minutes, with external cooling (0-5 ºC). *N,N*-Dimethylaniline (0.015 mL, 0.12 mmol) was dissolved in water (0.3 mL) and H_2SO_4 (1 drop), and this was added the diazonium solution slowly, external cooling at 0 ºC and left stirring for 45 minutes. The solid was a complex mixture (by ^1H nmr in DMSO-d_6) and was not further purified due to the low solubility in most common solvents.

Method 2. To a cold suspension of imidazole **3a** (0.050 g, 0.22 mmol) in HCl (36%, 1 mL), an aqueous solution (1 mL) of sodium nitrite (0.015 g, 0.22 mmol) was added dropwise and the mixture was kept stirring for 15 minutes. To a solution of *N,N*-dimethylaniline (0.028 mL, 0.22 mmol) in a mixture of glacial acetic acid/water 1:1 (1 mL) the diazonium salt was added at low temperature (0-5ºC) and the mixture was stirred over night. The precipitate was collected by filtration. The solid was a complex mixture (by ^1H nmr in DMSO-d_6) and was not further purified due to the low solubility in most common solvents.

Method 3. Imidazole **3a** (0.10 g; 0.44 mmol) was partially dissolved in HCl 1 *N* (1.5 mL) at 0-5 ºC (ice bath), an aqueous solution (1.5 mL) of potassium nitrite (0.037 g, 0.44 mmol) was added dropwise and was kept stirring for 15 minutes. A solution of 3-*N,N*-dimethylaniline (0.061 g, 0.48 mmol) in glacial acetic acid and water 1:1 (5 mL) was added dropwise at 0-5 ºC to the

diazonium salt suspention. The reaction was allowed to warm to room temperature overnight, and the solid was collected by filtration, washed and dried. The solid was a complex mixture (by ^{1}H nmr in DMSO-d_6) and was not further purified due to the low solubility in most common solvents.

Method 4. A cold aqueous solution (5 mL) of sodium nitrite (0.3 g, 4.38 mmol) was added with stirring to a suspension of imidazole **3a** (0.5 g; 2.19 mmol) in glacial acetic acid (0.5 mL). The suspension was kept stirring at low temperature (< 5 ºC) for 35 minutes. The reaction mixture was added to a solution of *N,N*-dimethylaniline (0.028 mL; 4.38 mmol) in glacial acetic acid and water 1:0.5 (12.5 mL) and was stirred at room temperature for 30 minutes.

The solid was collected by filtration and washed with cold water and the mother liquor was extracted with ethyl acetate. Both the solid and the mother liquor were purified by column chromatography with diethyl ether/light petroleum and ethyl acetate/ diethyl ether (mixtures of increasing polarity). Compounds **10**, **11** and **12** were isolated and identified.

3-[(*N,N*-Dimethylaminophenyl)-4'-diazenyl]-benzoic acid (10). It was obtained as an orange solid, 0.042 g (7%), R_f 0.27 (ethyl acetate–hexane 6:4). ^{1}H and ^{13}C spectroscopic data compared well with those of a genuine sample [13].

4-Nitroso-*N,N*-dimethylaniline (11). This compound was obtained as a green solid, 0.124 g (19%), mp 78.6-80.6 ºC, R_f 0.56 (ethyl acetate–hexane 6:4). ^{1}H and ^{13}C spectroscopic data compared well with literature [23b].

4-Nitro-*N,N*-dimethylamine (12). This compound was obtained as an orange solid, 0.028 g (4%), mp 78.6-81.5 ºC, R_f 0.73 (ethyl acetate-hexane 6:4). ir (KBr 1%): ν 2954, 2923, 2854, 1726, 1599, 1536, 1514, 1461, 1376, 1161, 881, 856, 812, 755, 721 cm^{-1}. ^{1}H nmr ($CDCl_3$): δ 3.11 (s, 6 H, NMe_2), 6.60 (d, 2 H, 2-H and 6-H, J = 9.6 Hz), 8.12 (d, 2 H, 3-H and 5-H, J = 9.6 Hz) ppm. ^{13}C nmr ($CDCl_3$): δ 40.2 (NMe_2), 110.2 (C-2 and C-6), 126.1 (C-3 and C-5) ppm. These values compared with the literature data [23c] of analogous compounds. ms (EI): *m/z* (%) 167 (M^++1, 11), 166 (M^+, 98).

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