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Synthesis and Characterization of Some New Aminoimidazoles

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Some new arylimidazoles and formimidoyl-1H-imidazoles derivatives have been synthesized in good yields by reaction between formamidines and base. The anilinium chloride is believed to act as a general acid catalyst and results in a significant acceleration of the rate of reaction. All these derivatives have been characterized basis of IR and ^{1}H and ^{13}C NMR spectral studies.

Key Words: Formimidoyimidazole, Imidazole, Amidine, Diaminomaleonitrile.

INTRODUCTION

Starting from readily available ethyl (Z)-N-(2-amino-1,2- dicyanovinyl)formimidate, N-aryl-N'-[2-amino-1,2-dicyanovinyl]-formamidines (**2**) can be prepared in good yields by reaction with aromatic amines at room temperature in the presence of an acid catalyst. ^{1}H NMR spectra of these amidines in DMSO show evidence for configurational equilibrium which, on the basis of nuclear overhauser effect (NOE) experiments, appears to be due to rotation about the C4-N3 bond rather than prototropic tautomerism. Treatment of the amidines with a base (DBU) at room temperature gave the corresponding 5-amino-1-aryl-4-(cyanoformimidoyl)-1H-imidazoles (**3**) in high yield, whereas reaction with KOH solution afforded the respective 5-amino-4-cyano-1-arylimidazoles (**4**). These last compounds can also be prepared from 3 by reaction with KOH solution.

5-Amino-4-cyanoimidazoles have long been recognized as useful synthetic precursors to purines, but there is no simple, general synthesis available for 1-aryl derivatives of these compounds. Sen and Mukhopadhyay[1] reported the preparation of 5-amino-4-cyano-1-(*p*-aminosulfonyl phenyl)-imidazole *via* a multistep synthesis from the corresponding 1-methyl derivative. Frank and Zeller[2] have described the synthesis of a number of 1-aryl- and 1-heteroaryl-5-amino-4-cyanoimidazoles (aryl = 2- and 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,4-$Me_2C_6H_3$; heteroaryl = 2- and 3-pyridyl, 5-Cl-2-Pyridyl,

3,5-diCl-2-pyridyl, 2-Cl-3-pyridyl and 2- pyrimidine) in low to moderate yields by reaction of the corresponding ethyl N-substituted formimidate with 2-aminomalodinitrile tosylate in acetic acid.

In this paper, we have been interested in the chemistry of diaminomaleonitrile (DAMN) and its derivatives, in particular, ethyl-2-(2-amino-1,2-dicyanovinyl)formimidate (**1**)[3-5] which can be prepared in good yield from the reaction between DAMN and triethyl orthoformate in dioxane[6]. From the previous work[6] it appeared that **1** would be a useful starting material for the preparation of new N-aryl-N'-[2-amino-1,2-dicyanovinyl]-formamidines (**2**). It was envisaged that these could be readily converted into 5-amino-1-aryl-4-(cyanoformimidoyl)-1H-imidazoles (**3**), which are expected[7-14] to be useful precursors to new 6-carbamoyl-1, 2-dihydropurines and 6-substituted purines derivatives[15-17]. In addition, **2** could provide a simple route to the desired 5-amino-1-aryl-4-cyanoimidazoles (**4**). The results of this investigation are now reported.

EXPERIMENTAL

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

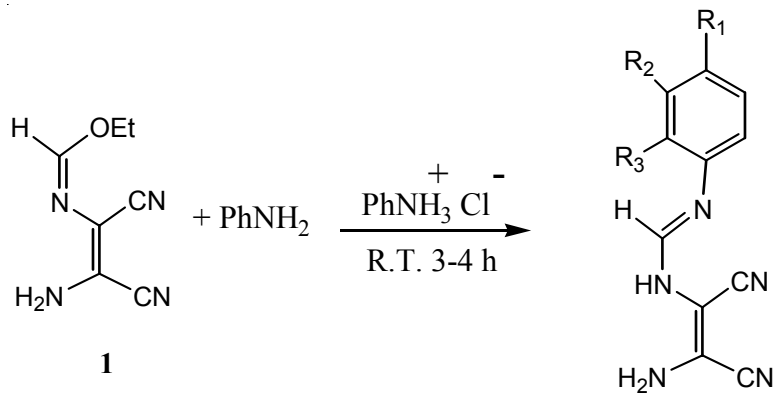
General procedure for the preparation of N-Aryl-N'-[2-amino-1,2-dicyanovinyl]formamidines (2a-c): The aromatic amine (5.64 mmol) was added to a suspension of 1 (5.62 mmol) in dry ethanol or ethyl acetate, which contained anilinium chloride (0.02 g). The mixture was stirred at room temperature until TLC showed that all the formimidate had disappeared (usually 3 to 4 h) and the amidine was isolated by filtration. In a few cases precipitation had to be assisted by concentrating the solution and addition of a 1:1 mixture of light petroleum and chloroform. In most cases the product was yellow to pale green. The precipitate was washed with diethyl ether or a light petroleum-chloroform mixture and was dried under vacuum to give the analytically pure product in the yields 62-95 %.

General procedure for the preparation of 5-amino-1-aryl-4-(cyanoformimidoyl)-1H-imidazoles (3a-c): To a stirred suspension of the formamidine (1.0 g) in either dry ethyl acetate, ethanol or a 1:1 mixture of ethyl acetate and isopropanol, was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (10 drops) and the reaction was monitored by TLC. The solid went into solution and after 1-3 h the product precipitated as an off-white to pale yellow solid. This was filtered, washed with diethyl ether or light petroleum and dried under vacuum to give the title compounds in the yields 88-93 %.

General procedure for the preparation of 5-Amino-1-aryl-4-cyanoimidazoles (4a-c): An aqueous solution of 1 M potassium hydroxide (1 mL) was added to a suspension of the formamidine (1 mmol) in ethanol (1 mL) and the mixture was stirred at room temperature for *ca*. 1 h. The white solid which precipitated was washed with water, a few drops of ethanol and finally diethyl ether before drying under vacuum. The yields of these reactions were 75-90 %.

RESULTS AND DISCUSSION

Treatment of **1** with an equimolar amount of the appropriate aromatic amine at room temperature in ethanol in the presence of a catalytic amount of anilinium chloride afforded the corresponding formamidines **2a-c** in 62-95 % yields based on isolated product. In these cases, isolation is achieved by simple filtration of the product mixture and little or no further purification is required to give analytically pure products. The anilinium chloride is believed to act as a general acid catalyst and result in a significant acceleration of the rate of reaction. When it is absent, appreciable decomposition occurs and the amidine product becomes difficult to isolate from tarry by-products with consequent low yields. The amine hydrochloride salts of the arylamine reactions also catalyze these reactions, but it is often more convenient to use the anilinium salt.



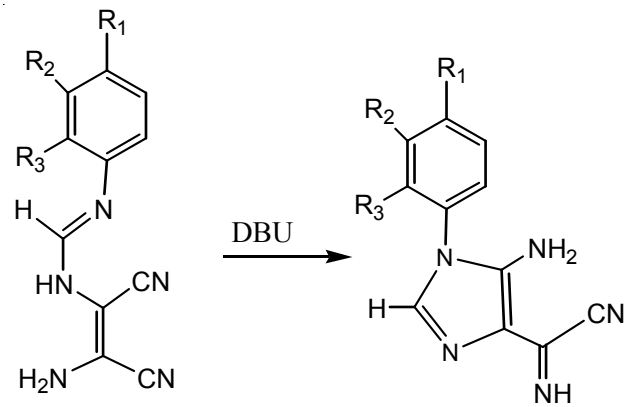
1 **2a-c**

a : R_1 = Me, R_2=R_3= H
b : R_1= R_3=Me, R_2= H
c : R_1=R_3=H, R_2= Me

^{1}H NMR spectra of compounds **2a-c** in dimethyl sulfoxide had some interesting features. The HC=N proton was a multiplate, at δ 7.1-7.7 ppm and showed coupling with protons aromatic ring. NH proton appeared as a

broad singlet at 8.1-9.9 ppm and was confirmed by D_2O exchange. The infrared spectrum of amidine **2a-c** showed two strong absorption in the region 2210-2225 cm^{-1} characteristic of CN stretching vibrations, together with an NH and a C=N stretching vibration at 3100-3460 and 1610-1640 cm^{-1}, respectively.

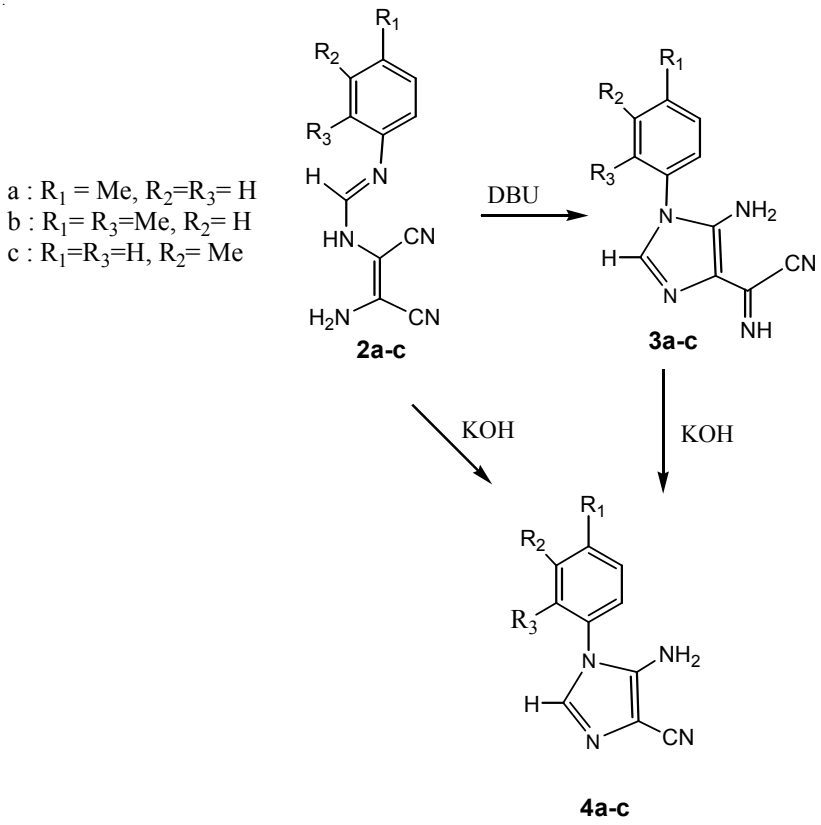
When several drops of DBU are added to a suspension of the amidines **2a-c** in ethyl acetate or ethanol, cyclization occurs in 1-3 h to give the corresponding 5-amino-1-aryl-4-(cyanoformimidoyl)imidazoles (**3a-c**) in good yields (88-93 %). All the compounds were obtained in an analytically pure state and IR band show a strong band in the 2200-2230 cm^{-1} region for a C=N bond and C=N stretching vibrations within the region of 1660-1650 cm^{-1}. In all cases the signals were sharp and in the ^1H NMR spectra the CH proton of the imidazole ring appears in the range δ 7.4-7.7, the NH_2 protons at δ 6.5-6.9 and the =NH proton at δ 11.0-11.3 ppm.



2a-c **3a-c**

a : R_1 = Me, R_2=R_3= H
b : R_1= R_3=Me, R_2= H
c : R_1=R_3=H, R_2= Me

When a saturated solution of KOH in ethanol is added to a suspension of the amidines **2a-c** in an alcohol at room temperature this affords the corresponding 5-amino-1-aryl-4-cyanoimidazoles (**4a-c**) in good yields (75-90 %). These compounds can also be made in comparable yield by the reaction of the compounds **3a-c** with a saturated solution of KOH in ethanol under conditions similar to those described above.



Compounds **4a-c** were recrystallized from mixture of ethanol/methanol (1:1) and gave pale yellow to off white crystals, respectively. These were fully characterized by TLC, IR and ^{1}H NMR spectroscopy. The infrared spectrum confirmed the presence of the NH and C=N stretching vibrations within the region of 3100-3400 and 1650-1660 cm^{-1}, respectively. The infrared spectrum also showed a sharp absorption band within the range of 2200-2220 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 5.6-6.6 ppm and in several cases the assignment were confirmed by D_2O exchange. The proton of the imidazole ring appeared as a sharp singlet in the range of 7.1-7.4 ppm.

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