

Guanidine: studies on the reaction with ethyl *N*-(2-amino-1,2-dicyanovinyl)formimidate

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**Dedicated to Professor António M. d'A. Rocha Gonsalves
on the occasion of his 70th birthday**

DOI: <http://dx.doi.org/10.3998/ark.5550190.0011.509>

Abstract

Formimidate **1** was reacted with guanidinium chloride, at room temperature, in the presence of sodium ethoxide and in dilute THF solution, leading to pyrimidine **10** by an unusual intramolecular cyclization process. A different reaction mechanism operated when imidate **1** was combined with guanidinium acetate in nitromethane under reflux. Structure **14** is tentatively assigned to this new product.

Keywords: Guanidine, pyrimidine, imidazole, triazepine, cyclization

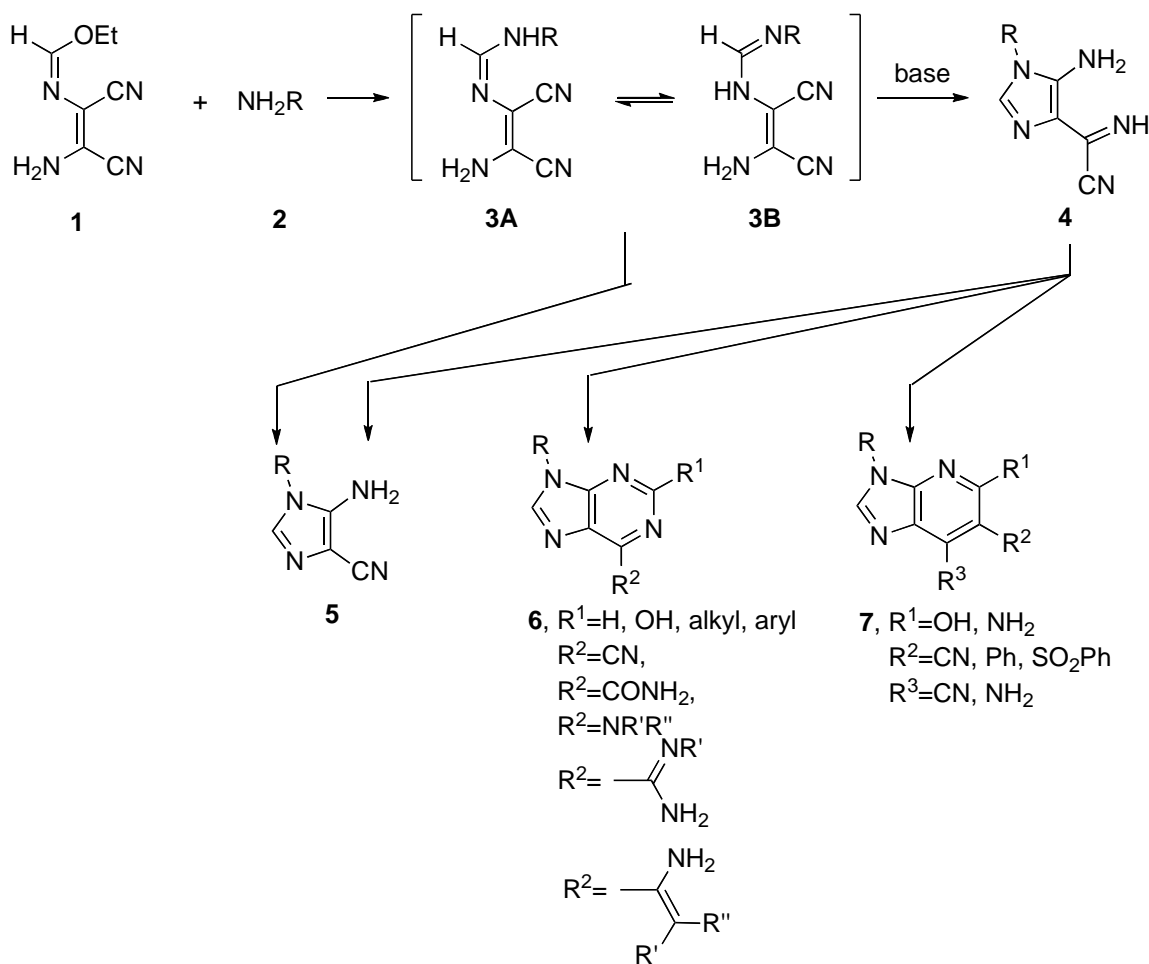
Introduction

Guanidine, a nitrogen organic base, has been widely used in the synthesis of heterocyclic compounds incorporating at least two nitrogen atoms. This moiety is present in the side-chain of the amino acid arginine and plays an important role in the interaction with enzymes or receptors through hydrogen bonding and/or electrostatic interactions.¹

Compounds incorporating a guanidine moiety have been isolated from various microorganisms² and proved to be biologically active either as antimicrobial,³ antiviral⁴ or antifungal⁵ agents. The synthesis of compounds incorporating the guanidine unit, including analogs or derivatives of natural products, is considered an important approach to the design of new drug candidates.

In our research group, a versatile and simple synthetic method was developed for the preparation of highly functionalized imidazoles. The initial step of the reaction sequence (Scheme 1) is the formation of an amidine **3** from the reaction of imidate **1** and a primary amine **2**. Ammonia,⁶ alkyl⁷ and aryl⁸ amines, hydrazines⁹ and hydroxylamine ethers¹⁰ have successfully

been used in this reaction and the resulting amidine was isolated in two different tautomeric forms (**3A** and **3B**). A combination of different configurations can also be envisaged for the amidine function but this seems to have little influence on the intramolecular cyclization reaction to generate the substituted imidazole **4** or **5** upon addition of base.



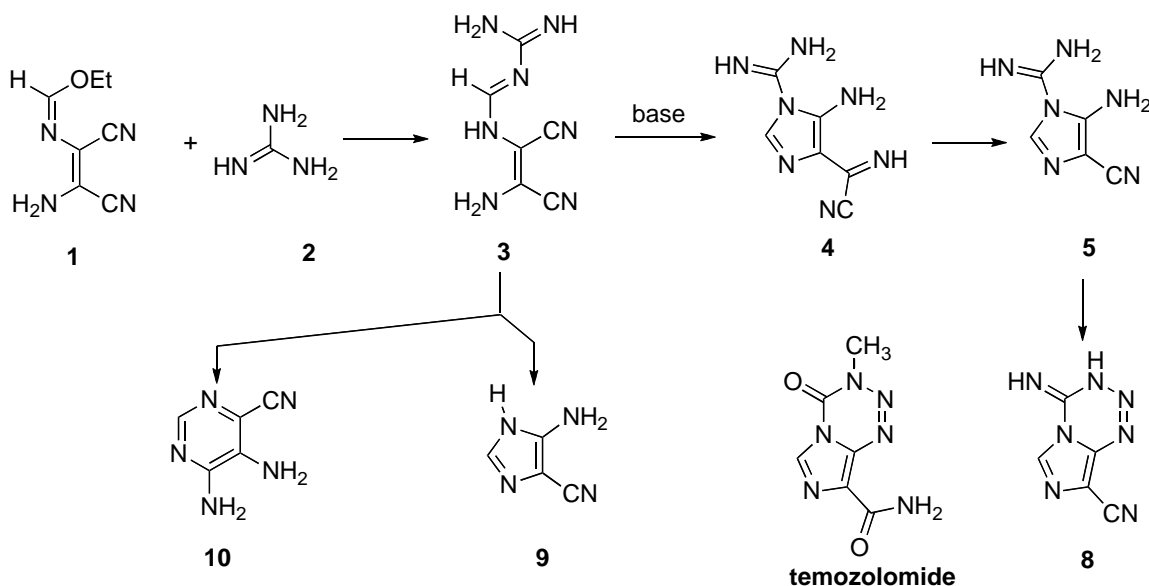
Scheme 1

Mild basic conditions usually allow the isolation of imidazole **4**, where the reactivity of the 5-amino and 4-cyanoformimidoyl substituents has been widely explored. The regioselective synthesis of purine derivatives **6** has been reported and allowed the preparation of 6-cyano,¹¹ 6-carbamoyl,⁶ 6-amidino,¹² 6-amino¹³ and 6-enamino purines.¹⁴ Functionalized imidazo[4,5-*b*]pyridines **7** were also produced¹⁵ upon reaction with various carbon acids.

Imidazoles **5** are formed in the presence of a stronger base (usually aqueous sodium hydroxide solution) either directly from amidine **3** or from imidazole **4**, after elimination of HCN. Compounds **5** are also considered important precursors of substituted purines and of other imidazole-fused heterocycles, generated through the *o*-amino-nitrile functionality.

Results and Discussion

The synthetic versatility of the easily accessible amidines **3** and the biological importance of the guanidine substituent, prompted us to study the reaction of imidate **1** with guanidine (Scheme 2), aiming at the synthesis of amidine **3** ($R = C=NH(NH_2)$).



Scheme 2

This amidine was expected to evolve to the corresponding imidazole **5** upon addition of base. Diazotization of **5** in aqueous acid would ultimately lead to compound **8**, an analogue of temozolomide, an imidazotetrazine derivative with antineoplastic activity.¹⁶

Guanidine is commercially available as a salt and in the present work the hydrochloride salt was used. Liberation of the free guanidine was performed *in situ*, by addition of base to the reaction mixture. The reaction was carried out in a 1.2 – 1.5 mmolar scale, using various solvents (ethanol, THF, nitromethane, DMF) and various bases (DBU, triethylamine, sodium ethoxide). The reaction (followed by tlc) was very slow, leading to complex reaction mixtures and/or extensive degradation (Table 1, entries 1-5). Pyrimidine **10** was isolated in 30% yield from a dark brown solution when the hydrochloride salt of guanidine (1.2 mmoles) was neutralized with an ethanolic solution of sodium ethoxide in THF (4.5 mL). The reagents were consumed after 35 minutes at room temperature, and the product precipitated from solution as an off-white solid (Table 1, entry 7). The extensive polymerization could be avoided by using a dilute solution, under the experimental conditions summarized in entry 8 (Table 1). When the same reagents were combined in 50 mL of THF, pyrimidine **10** was the major product, isolated in 87% yield.

These results indicate that the base strength is an important issue in the formation of a pure product. The use of triethylamine or DBU leads to a very slow reaction between guanidine **2** and

imidate **1** probably due to the low concentration of primary amine that is generated. Under these circumstances, a diversity of side-reactions is responsible for the consumption of the reagents, leading to the complex mixtures that were observed. The use of a stronger base (sodium ethoxide) led to a much faster reaction, ultimately allowing the isolation of a pure product in an excellent yield (entry 8).

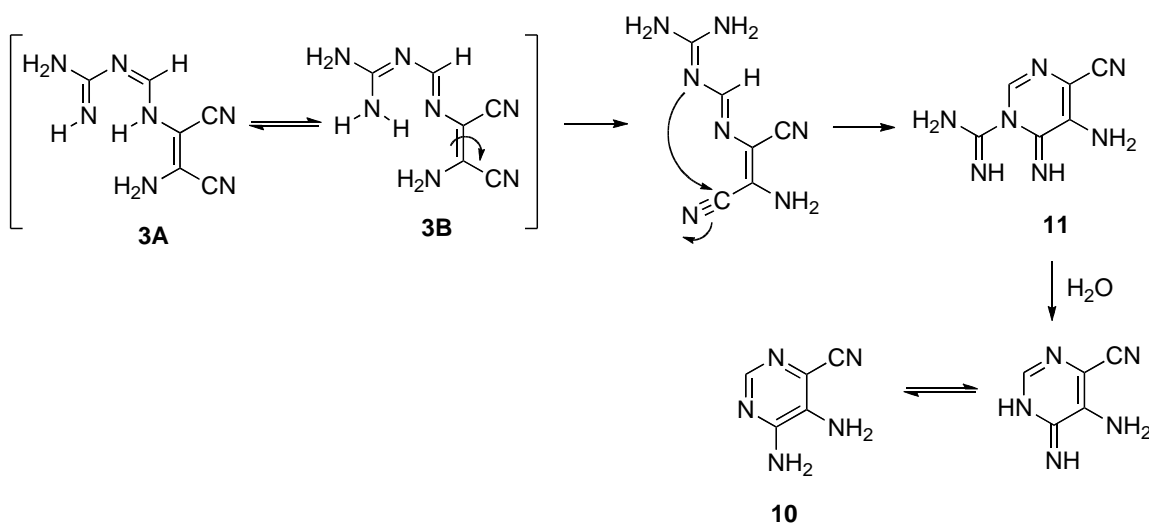
The formation of pyrimidine **10** can be explained if we consider that amidine **3** was formed (Scheme 3) and rapidly cyclised intramolecularly in a process that is self catalyzed by guanidine, acting simultaneously as a nucleophile and as a base. In dilute THF solution, extensive intramolecular hydrogen bonding decreases the double bond character of the alkene moiety, facilitating rotation around this bond and placing the cyano group in a convenient position for nucleophilic attack by the amidine nitrogen. The amidine substituent in intermediate **11** is susceptible to hydrolysis and is cleaved by traces of moisture in the solvent, ultimately leading to the isolated product **10**.

Table 1. Selection of experimental conditions for the reaction of guanidine with ethyl *N*-(2-amino-1,2-dicyanovinyl)formimidate

Entry	Reaction conditions	Product(s) (yield)
1	2.HCl:1 (1.3:1); DBU (1.5 equiv.); nitromethane (2 mL); 32 days, rt	Complex mixture ^a
2	2.HCl:1 (1.3:1); DBU (2 equiv.); DMF (1 mL); 4 days, rt	Complex mixture ^a
3	2.HCl:1 (1.3:1); NEt ₃ (2 equiv.); DMF (1 mL); 4 days, rt	Complex mixture ^a
4	2.HCl:1 (1:1); DBU (1 equiv.); 6.2 mL EtOH:THF (1:4); N ₂ atmosphere, 60 days, 0 °C	Complex mixture ^a
5	2.HCl:1 (1.3:1); DBU (1 equiv.); 6 mL EtOH:THF (1:5); 78 days, rt	Complex mixture ^a
6	2.HCl:1 (1:1); DBU (1.5 equiv.); 8 mL EtOH:THF (1:7); N ₂ atmosphere, 72 days, 10 °C	9 (4%) 10 (2%)
7	2.HCl:1 (1:1); NaOEt/EtOH (1 equiv.); THF (4.5 mL); N ₂ atmosphere, 35 min., rt	10 (30%)
8	2.HCl:1 (1:1); NaOEt/EtOH (1 equiv.); THF (50 mL); 35 min., rt	10 (87%)

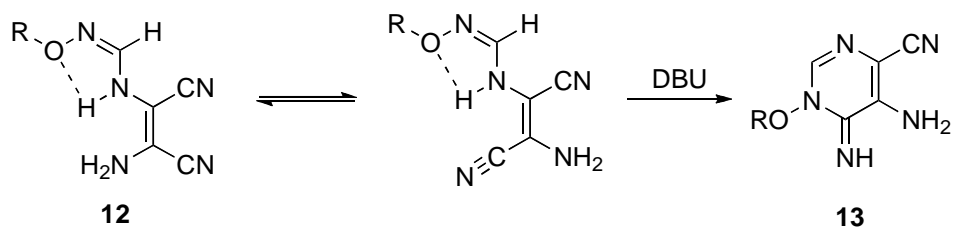
^a After dry flash chromatography of the crude reaction mixture.

The formation of imidazole **9**,⁶ isolated in only 4% yield in one of the experiments (Table 1, entry 6) indicates that the expected reaction sequence is also occurring, leading to the formation of compound **5** (Scheme 2). Rapid cleavage of the amidine substituent on N-1 leads to the unsubstituted imidazole **9**.



Scheme 3

The cyclization of amidine **3** to generate a pyrimidine ring is an unusual situation previously observed in the reaction of imidate **1** with amidoxime ethers.¹⁰ The reaction is believed to proceed through a similar mechanism, as a result of intramolecular hydrogen-bonding involving the N-hydrogen and the amidoxime oxygen atom (**12**, Scheme 4). X-Ray analysis confirms the presence of the intramolecular hydrogen-bond in the crystal structure of amidoxime **12** (R=CH₂Ph). X-Ray analysis of the final product **13** also confirms the structure assignment, where the absence of a tautomerizable proton on a ring nitrogen, prevents the formation of the fully aromatic pyrimidine.

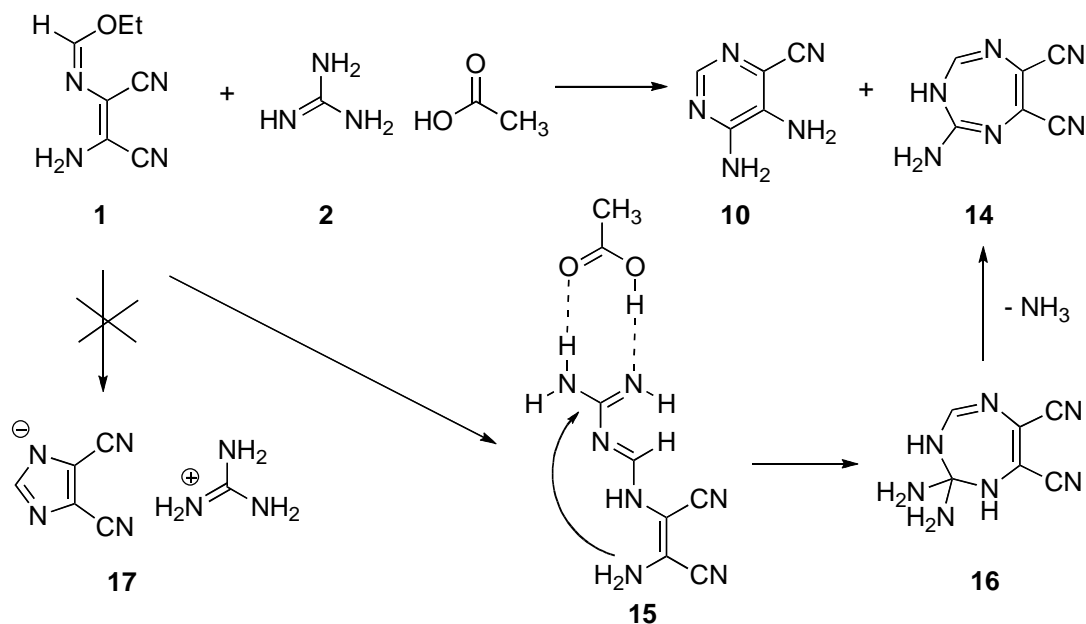


Scheme 4

In an attempt to isolate the amidine **3**, imidate **1** was combined with one molar equivalent of the acetate salt of guanidine **2** and the mixture was heated at reflux in THF and nitromethane

(5:1) for 30 h. Pyrimidine **10** was again isolated from the reaction mixture (37%), but another compound, tentatively identified as the triazepine **14** (61%), was formed as the major product (Scheme 5). Refluxing equimolar amounts of imidate **1** and the acetate salt of guanidine **2** in nitromethane for 6 h led to the isolation of compound **14** in 89% yield.

The structures assigned to compounds **10** and **14**, supported by spectroscopic data, were consistent with their elemental analyses. This information was crucial, as only one C–H proton is present in the ^1H NMR spectrum of these compounds. Sharp singlets at δ 7.75 ppm (**10**) and δ 7.77 ppm (**14**) were assigned to this proton. The N–H signals are visible in the spectra of both compounds. Two singlets integrating for two protons ($2\times\text{NH}_2$) at δ 6.00 and 7.15 ppm are indicative of the presence of two amino groups in compound **10**. For compound **14**, a singlet at δ 6.90 ppm, integrating for three protons, was assigned to the NH_2 and NH signals, probably due to extensive tautomerism of the ring N–H proton. In the ^{13}C NMR spectra, the signal assigned to the C–H carbon is visible at δ 147.0 ppm for compound **10** and at δ 145.4 ppm for compound **14**. The signal for the cyano group is present in the spectrum of **10** (δ 116.7 ppm) but is may be absent in the spectrum of **14**. The signals at δ 114.1 and 116.3 ppm are equally intense in the spectrum of this compound and were assigned to the ring carbon atoms adjacent to each cyano group. As can be seen in the ^{13}C NMR data for this compound, only two signals are present that could either be assigned to the two cyano groups or to the adjacent carbon atoms (d 114.1 and 116.3 ppm). Correlation techniques (HMBC and HMQC) allowed the identification of C–H (d 148.5 ppm) and this signal shows an intense 3-bond correlation with the signal at d 116.3 ppm and a faint correlation with the signal at d 114.1 ppm (interpreted as a 4-bond correlation). These two equally intense signals can be assigned to the ring carbon atoms but they could equally belong to the ring carbon (d 116.3 ppm) and the adjacent cyano group (d 114.1 ppm). If we consider that the two ring carbons have a similar chemical environment, they may lead to coincident signals, and the same applies to the two cyano groups. In the IR spectrum, the presence of one intense band at ν 2225 cm^{-1} in the IR spectrum for compound **10** and of two intense bands at ν 2239 and 2221 cm^{-1} for compound **14**, assigned to the nitrile stretching vibration, confirms the presence of this functional group in both compounds.



Scheme 5

The formation of compound **14** can be explained if a stable ion pair **15** is formed, involving the guanidine and acetate units (Scheme 5). This effect would enhance the electrophilic character of the guanidine carbon, leading to compound **16** upon intramolecular interaction with the amino group. This intermediate would evolve to the isolated product **14** after elimination of ammonia. Intramolecular cyclization of imidate **1** to generate the 4,5-dicyanoimidazole is known to occur when this compound is refluxed in dioxane for a few hours.¹⁷ If this pathway was operating under the present reaction conditions, the guanidinium salt **17** would be isolated. This possibility was excluded by the synthesis of **17** from the commercially available imidazole and the hydrochloride salt of guanidine, after neutralization with sodium ethoxide. The white solid isolated showed a single intense band at ν 2229 cm^{-1} in the IR spectrum, assigned to the CN stretching vibration of the two geometrically equivalent functional groups. In the ^1H NMR spectrum, the signal for the C-H proton was a sharp singlet at δ 7.33 ppm and a singlet integrating for eight protons at δ 6.93 ppm indicated that the six N-H protons ($3\times\text{NH}_2$) of the guanidinium counterion overlap with the two protons for the hydration molecule present in the salt and confirmed by elemental analysis. In the ^{13}C NMR, a total of four signals were registered. This confirms the symmetrical nature of the molecule, where the negative charge is delocalized over the imidazole ring. Carbon atoms C4 and C5 are equivalent and the same applies to the two cyano groups (d 116.6 and d 117.4 ppm).

Conclusions

The present study on the reaction of formimidate **1** with guanidine, showed that the reaction did not follow the usual pathway, where imidazole **5** ($\text{R} = \text{C}=\text{NH}(\text{NH}_2)$) was expected upon

intramolecular cyclization. The highly functionalized pyrimidine **10** was isolated when imidate **1** was combined with the hydrochloride salt of guanidine, at room temperature, in dilute THF solution and in the presence of an equimolar amount of sodium ethoxide. Under reflux conditions in nitromethane and using guanidinium acetate, a different product was formed, tentatively identified as the triazepine **14**.

Experimental Section

Reaction of ethyl *N*-(2-amino-1,2-dicyanovinyl)formimidate (**1**) with guanidinium chloride in the presence of base

Method A. Guanidinium chloride (0.11 g, 1.20 mmol) was combined with a 0.45 M ethanolic solution of sodium ethoxide (2.7 mL, 1.20 mmol). The white solid precipitate (NaCl) was filtered off and washed with THF (0.5 mL). The solution was kept under a nitrogen atmosphere, in a round-bottomed flask equipped with a magnetic bar and a serum cap. Imidate **1** (0.20 g, 1.20 mmol), prepared according to an experimental procedure described in the literature,¹⁷ was dissolved in THF (45 mL) and the solution added dropwise with a syringe, through the serum cap. The pale orange reaction mixture was efficiently stirred at room temperature for 30 min.. The solid suspension was filtered and washed with diethyl ether to give 4,5-diamino-6-cyanopyrimidine **10** (0.14 g, 1.04 mmol, 87%) as a cream solid which required no further purification: mp above 300 °C; IR (Nujol mull) 3394, 3222, 3104, 2225, 1689, 1651, 1564, 1524 and 1377 cm⁻¹; ¹H-NMR (300 MHz, DMSO-*d*₆) δ 6.00 (s, 2H, NH₂), 7.15 (s, 2H, NH₂), 7.75 (s, 1H, CH); ¹³C-NMR (75 MHz, DMSO-*d*₆) δ 113.1 (C6), 116.7 (CN), 133.0 (C5), 147.0 (C2), 153.6 (C4); Anal. Calcd. for C₅H₅N₅: C, 44.4; H, 3.7; N, 51.8%. Found: C, 44.6; H, 3.8; N, 51.7%.

Method B. Guanidinium chloride (1.15 g, 1.57 mmol) was dissolved in ethanol (1 mL), combined with DBU (1 molar equivalent) and the mixture was stirred at room temperature for 30 min. A solution of imidate **1** (0.20 g, 1.22 mmol) in THF (5 mL) was added to the ethanolic solution which was stirred at 10 °C for 72 days, at which point the imidate was no longer present (tlc). Dry flash chromatography of the dark product mixture using diethyl ether followed by ethyl acetate as eluents, led to a cream solid identified as 4,5-diamino-6-cyanopyrimidine **10** (4.1 mg, 0.03 mmol, 2%) isolated from the ether extract. An off-white solid was isolated from the crop eluted with ethyl acetate. This compound was identified as 5-amino-4-cyanoimidazole **9** (5.5 mg, 0.05 mmol, 4%). The ¹H- and ¹³C-NMR spectra of compound **9** were in agreement with the literature values:⁶ ¹H-NMR (300 MHz, DMSO-*d*₆) δ 6.10 (s, 2H, NH₂), 7.20 (s, 1H, CH), 11.6 (s, 1H, NH); ¹³C-NMR (75 MHz, DMSO-*d*₆) δ 93.8 (C4), 121.8 (CN), 134.4 (C2), 152.0 (C5).

Reaction of ethyl *N*-(2-amino-1,2-dicyanovinyl)formimidate (**1**) with guanidinium acetate in the absence of base

Guanidinium acetate (0.22 g, 1.83 mmol) was combined with imidate **1** (0.30 g, 1.83 mmol) in nitromethane (20 mL) and the solution was heated at reflux for 6 h, when the imidate was completely consumed (tlc). The dark suspension was filtered hot, and the filtrate was concentrated in the rotary evaporator. Addition of diethyl ether led to a cream solid which was filtered off and washed with diethyl ether. The product was assigned structure **14** (0.26 g, 1.63 mmol, 89%) and required no further purification: mp = 145-147 °C; IR (Nujol mull) 3484, 3418, 3391, 3359, 3128, 2239, 2221, 1675, 1658, 1459 and 1445 cm⁻¹; ¹H-NMR (400 MHz, DMSO-d₆) δ 6.90 (s, 3H, NH₂ + NH), 7.77 (s, 1H, CH); ¹³C-NMR (100 MHz, DMSO-d₆) δ 114.1, 116.3, 145.4 (CH), 157.9; Anal. Calcd. for C₆H₄N₆.0.4 H₂O: C, 43.07; H, 2.87; N, 50.24%. Found: C, 42.99; H, 3.18; N, 50.32%.

Synthesis of the guanidinium salt of 4,5-dicyanoimidazole

Guanidinium chloride (0.13 g, 1.38 mmol) was combined with a 0.46 M ethanolic solution of sodium ethoxide (3.0 mL, 1.38 mmol). The white solid precipitate (NaCl) was filtered and washed with ethanol (1 mL). 4,5-Dicyanoimidazole (0.16 g, 1.38 mmol) was added to the previous solution, which was stirred at room temperature for 15 min. The solvent was partially removed in the rotary evaporator and addition of dichloromethane led to a white solid that was filtered and washed with dichloromethane. The product was identified as **17** (0.20 g, 1.13 mmol, 82 %): IR (Nujol mull) 3524-3000 (multiple, overlapped bands), 2229, 1660, 1459, 1376, 1300 and 1108 cm⁻¹; ¹H-NMR (300 MHz, DMSO-d₆) δ 6.93 (s, 8H, 3xNH₂ + H₂O), 7.33 (s, 1H, CH); ¹³C-NMR (75 MHz, DMSO-d₆) δ 116.6, 117.4, 148.5 (CH), 157.9; Anal. Calcd. for C₆H₇N₇.1.2H₂O: C, 36.25; H, 4.73; N, 49.35%. Found: C, 36.45; H, 4.81; N, 49.44%.

Acknowledgements

This work was supported by the University of Minho and by Fundação para a Ciência e a Tecnologia through project PCDT/QUI/59356/2004.

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