C-N Bond forming reactions in the synthesis of substituted 2-aminoimidazole derivatives

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Dedicated to Professor Rosa Claramunt on the occasion of her 65th birthday

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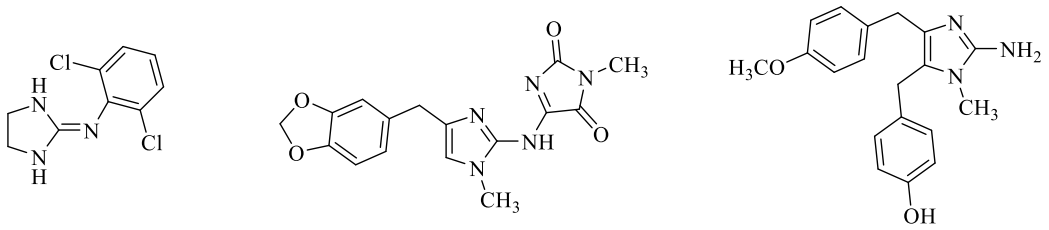
Abstract
Carbon-nitrogen bond forming reactions oriented to the synthesis of 2-amino-imidazolidines and imidazoles have been investigated. The C-2 amination of imidazolidinones, *via* the corresponding 2-chlorodihydroimidazoles, led to 2-benzylaminodihydroimidazole or bis(dihydroimidazole)amino derivatives by choosing the adequate experimental conditions. On the other hand, the use of *N*-acyl-2-methylsulfanyldihydroimidazoles allowed carrying out the reactions with aromatic amines, such as *p*-anisidine. Finally, palladium catalyzed Buchwald-Hartwig amination was the method of choice for C-N coupling between 2-haloimidazoles and aromatic amines in the synthesis of the corresponding imidazoles.

Keywords: Imidazolidine, imidazole, amination, C-N bond forming reactions

Introduction

The 2-aminoimidazole or imidazoline moieties are important structural patterns present in natural and/or synthetic products that display a broad range of biological activities. For example, *Leucetta* and *Clathrina*-derived alkaloids, which have been isolated from marine sponges during the last three decades, were reported to exhibit antibacterial, anti-inflammatory, anticancer, and antiviral activity.[1-3] Different types of substituted 2-aminoimidazoles, including the pyrrole-2-aminomidazoles of the oroidin family and their synthetic analogs[4,5] possess anti-biofilm activities,[6,7]while 2-arylamino or iminoimidazolidines (*e.g.* clonidine), known hypertensive

agents,[8] have also been evaluated as α_2-adrenoceptor antagonists for the treatment of depression (Figure 1).[9-11]



Clonidine *Clathridine A* *Naamine A*

Figure 1

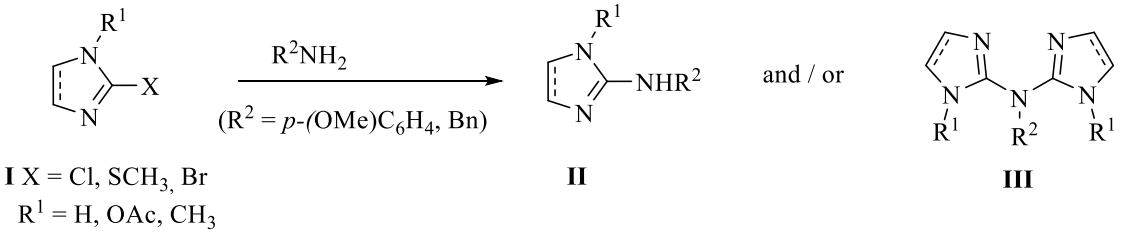
Several synthetic methods have been reported in the literature to obtain 2-aminoimidazoles that involve the construction of the heterocycle,[1] including the addition of substituted guanidines[12,13] or 2-aminopyrimidines (protected guanidines)[14] to α-haloketones, the base-mediated semi cleavage of hemiaminals obtained by reaction of *N*-Boc protected guanidines and *N*-carbomethoxy-1,2-dihydropyridines,[15] or the condensation of cyanamide and α-amino-ketones[16] or α-aminoesters.[6] In a similar way, the corresponding 2-aminoimidazolines have been synthesized by condensation of *N*-arylcarbonimidodithioates and ethylenediamine,[17,18] and by intramolecular cyclization of functionalized arylthioureas, obtained by reaction of isothiocyanatobenzene and ethylenediamine.[19,20]

A different approach relies in the late-stage introduction of the 2-amino group into imidazoles or imidazolines. Thus, the imidazole ring could be lithiated at C-2, followed by reaction with azides and subsequent reduction to obtain 2-aminoimidazoles.[21-26] However, this procedure requires several steps, and has failed in the synthesis of some natural products, such as kealiiquinone.[27] To solve these problems, Lovely group has recently developed a convenient procedure for the direct conversion of imidazolium salts into 2-aminoimidazoles by using *N*-chloroamides at room temperature.[27]

On the other hand, the synthesis of biologically active imidazolines, such as clonidine and indanazoline has been developed by Cussac et al. through the condensation between primary amines and imidazolidin-2-ones or 2-methylsulfanyldihydroimidazoles.[28-31] Other procedures involve the condensation of amines with dihydroimidazol-3-ium-2-sulfonate[32] or with protected imidazolidine-2-thione, though the last procedure requires the use of mercury (II) chloride.[9]

As part of our program to develop new procedures for the synthesis of heterocyclic systems,[33-35] we investigated several carbon-nitrogen bond forming reactions directed to the synthesis of 2-aminoimidazole derivatives. The aim was to achieve the amination at the C-2 position of both imidazole and imidazolidine moieties, avoiding metalation with strong (and potentially nucleophilic) bases. Thus, we studied the amination of imidazolidinones *via* the corresponding 2-chlorodihydroimidazoles (**I**, X = Cl), or 2-methylsulfanylhydroimidazoles (**I**,

X = SCH_3), and palladium catalyzed reactions of 2-haloimidazoles and amines (**I**, X = Br). Further, we were interested in the application of these procedures to the synthesis of bis-imidazolic systems, such as **III**, in one step (Figure 2).



I X = Cl, SCH_3, Br
R^1 = H, OAc, CH_3

II

III

Figure 2

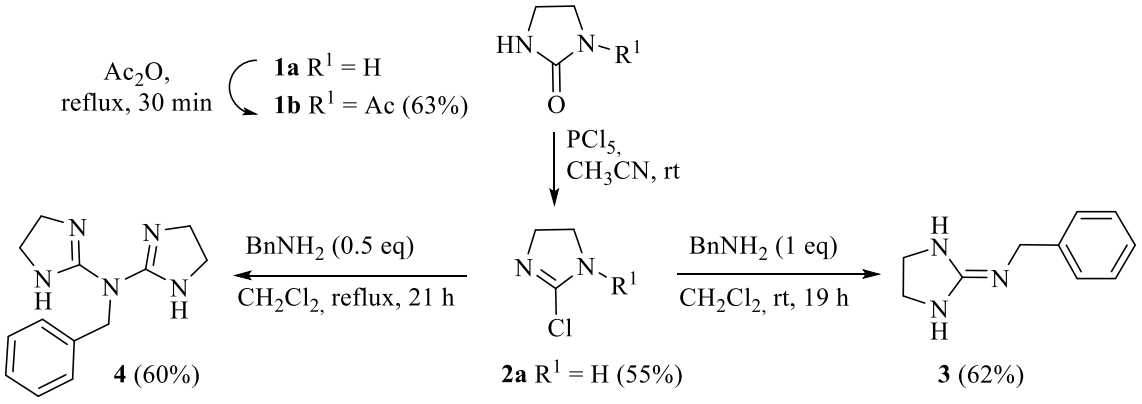
Results and Discussion

It is observed that a large number of bioactive alkaloids contain a central 2-aminoimidazole ring, substituted by one or two benzyl groups at various locations around the heterocyclic ring.[2] Although there are no examples of *N*-benzyl azoles, it should be interesting to prepare this type of derivative in order to test structure-activity relationships. On the other hand, it is very well-known that the presence of a 2-arylamino or imino group is an important structural key feature of pharmacophores, such as clonidine.[8] For this reason, we started our study with the synthesis of 2-aminoimidazolines **II** starting from 2-chlorodihydroimidazoles **I** (X = Cl) or their methylthio analogue (X = SCH_3) and using both benzylamine and *p*-anisidine. In this context, Cussac group has reported that 2-methylthioimidazolines can be converted into 2-iminoimidazolines by heating with primary amines. While this chemistry appears to work quite well, the alternative route of condensation of primary amines with *N*-acetylimidazolidin-2-one *via* its 2-chloro derivative formed *in situ* with $POCl_3$ only led to low to moderate yields (22-74%) of the *N*-acetylated imino derivatives.[28]

We began by using the commercially available imidazolidin-2-one (**1a**) as substrate. We first tried the one-pot procedure developed by Cussac and col., in which the chloride **2a** is generated *in situ* with $POCl_3$ in the presence of the amine. Although various reaction conditions were tested, this procedure always gave a sluggish reaction, providing a complex mixture of products. After some experimentation, we found that best results were obtained by stepwise conversion of the imidazolidin-2-one into the corresponding 2-chlorodihydroimidazole **2a**. This compound has been widely used in the synthesis of diverse heterocyclic structures,[36-38] and has been prepared mainly by chlorination of imidazolidine-2-thione.[39] The conditions outlined in Scheme 1 were the most effective overall for the subsequent reaction of **2a** with the primary amine to give 2-aminoimidazoline **3**. Thus, the 2-chloro derivative **2a** was efficiently obtained by treatment of imidazolidin-2-one **1a** with phosphorus pentachloride in acetonitrile at room temperature. The

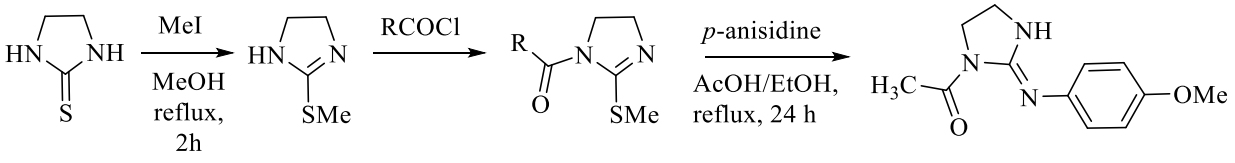
reaction with phosphorus oxychloride under various conditions was always sluggish. This chloride **2a** was immediately reacted with benzylamine in dichloromethane as solvent and at room temperature to give **3** in 62% yield. However, an interesting point arose when we came to perform the amination using the chloride **2a** in excess. Thus, treatment of the initially formed 2-chloro derivative **2a** (2 mmol) with benzylamine (1 mmol) in dichloromethane under reflux for 21 h led to benzyl bis(dihydroimidazole)amine **4** (60 %). It should be pointed out that bis(2-aminoimizadolines) with different linkers between the two heterocyclic rings show interesting pharmacological profiles when compare with the mono-imidazoline compounds.[11] Furthermore, these compounds could be considered as bidentate nitrogen ligands in transition-metal mediated C-C bond formation reactions.[40]

These conditions were tested on the *N*-acetylimidazolidinone **1b**, prepared by acetylation of the imidazolidinone **1a**.[41] However, all attempts using either benzylamine or *p*-anisidine always failed. Similar results were obtained when the one-step Cussac protocol was used.



Scheme 1

When we tried to extend the procedure to the use of aromatic amines, the procedure failed. Several exploratory sets of conditions were employed to carry out this transformation either using imidazolidinone (**1a)** or its *N*-acetyl derivative (**1b)**, but the results were very poor. Therefore, an alternative route involving amination of alkylthioimidazolidines was investigated. Thus, we decided to apply the procedure developed by Mundla et al.[29] to the *N*-acyl-2-methylthioimidazolines **7a-c** using *p*-anisidine.



Scheme 2

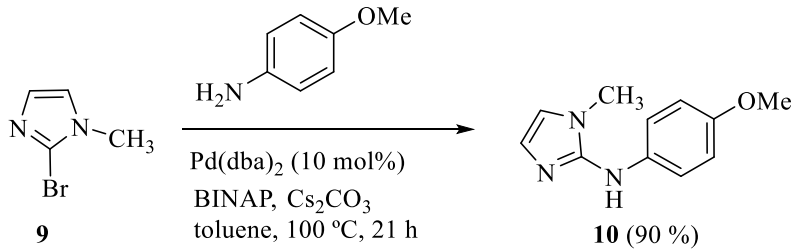
Synthesis of the target compounds **7a-c** began with imidazolidine-2-thione **5**, which was transformed into the corresponding 2-methylsulfanyldihydroimidazole **6** by treatment with methyl iodide in methanol under reflux (Scheme 2).[42] Compound **6** was easily acylated with Ac_2O, $ClCO_2CH_3$, or $ClCO_2Bn$ under standard conditions to the corresponding *N*-acyl derivatives **7a-c** in good yields.

We then undertook the C-2 amination. After some preliminary experiments on the *N*-acyl derivatives **7a-c** with *p*-anisidine, we settled on using *N*-acetyl derivative **7a** in AcOH (10%) / EtOH under reflux (Scheme 2), which provided the 2-arylimidazoline **8** in moderate yield. With the methoxycarbonyl (**7b**) and benzyloxycarbonyl (**7c**) derivatives we observed the formation of complex mixtures of products, probably due to hydrolysis of the carbamate moiety in the acidic reaction media and other unidentified side reactions. Other solvents were used (EtOH, dioxane), but no reaction was observed under these conditions. Although the reaction of the unprotected 2-methylsulfanyldihydroimidazole **6** with various primary alkyl amines has been reported,[28] no reaction was obtained when **6** was treated with benzylamine or *p*-anisidine. Thus, the use of methylsulfanyl derivatives such as **7a** allowed the amination reactions with aromatic amines under mild reaction conditions, but it required protection of the nitrogen atom of the imidazoline. However, this procedure did not allow the preparation of bis-(2-aminoimidazolines) when **7a** was used in excess.

1D and 2D NMR experiments allowed us to determine the predominant tautomeric form of these compounds. As expected, **3** and **8** exist as the imino tautomers, whereas the bis(guanidine) derivative **4** has perforce the 2-amino structure. In fact, the most characteristic signal for these compounds is the resonance of the quaternary carbon C-2 in the ^{13}C NMR, which appears at δ = 162.0 and 160.0 ppm for the imino tautomers **3** and **8**, respectively, and at δ = 127.7 ppm for the 2-amino derivative **4**. Besides, in the case of the 2-arylamino derivative **8**, the *ortho* aromatic protons are substantially more shielded (δ 6.84, d, *J* 8.9 Hz) than the *meta* protons (δ 7.10, d, *J* 8.9 Hz). In an amino tautomer all aromatic protons should absorb in a narrow range (6.33-6.74 ppm). These data are in full agreement with the predicted chemical shifts and the bibliographical data.[30,43]

Our next step was to replace the imidazolidine-amine unit by a 2-aminoimidazole. As stated above, introduction of the NH_2 group at the C-2 position of the imidazole ring has been carried out by a metalation/azide formation/reduction strategy, which requires a further alkylation step to provide access to the *N*-substituted derivatives.[21-26] Therefore, we sought for a more direct approach for the direct introduction of an arylamino group at C-2, which may also eliminate the use of strong bases. In this context, palladium-catalyzed amination methodologies for the formation of C–N bonds[44] were the method of choice. This procedure has been successfully applied mainly to benzo or hetero fused imidazole derivatives. Thus, the reaction of 2-chlorobenzimidazoles with 4-aminopiperidine led to the preparation of the antihistaminic norastemizole,[45] while a series of amide substituted purine derivatives were synthesized *via* palladium-catalyzed amidation reactions.[46] Thus, we set out to search for an adequate catalytic

system to achieve the C-N coupling between *p*-anisidine and 2-bromo-1-methylimidazole (**9**) (Scheme 3).



Scheme 3

Initial efforts to effect this palladium-catalyzed reaction employed the protocol developed by the Rizzo group[47] for the coupling of related substrates, 8-bromodeoxyguanosine derivatives: $Pd_2(dba)_3$ (10 mol%) as a catalyst in the presence of BINAP (30 mol%) with lithium hexamethyldisilazide as the base in toluene at 100 °C. However, in our case, a complex mixture of products was formed, and the 2-aminoimidazole could not even be detected. A series of bases was screened in an effort to develop a cleaner reaction. Gratifyingly, on changing the base to Cs_2CO_3, the C-N coupling product, *N*-aryl-1-methyl-1*H*-imidazole-2-amine (**10**), was obtained in very good crude yield (90%), based on ^{1}H NMR. However, this product was unstable and could not be purified by column chromatography. Because of the aromatic nature of the imidazole ring, this compound presents the 2-arylamino structure. In particular C-2 resonates at δ = 139.9 ppm in ^{13}C NMR, while the aromatic protons *meta* and *ortho* appear at δ 6.67, (d, *J* 9.0 Hz) and δ 6.72, (d, *J* 9.0 Hz), respectively.[43] Decreasing the catalyst loading led to a lower yield and conversion. It should also be mentioned that attempts to apply the procedure to the 2-bromoimidazole with a free NH group or to the corresponding 2-haloimidazolines always failed.

Conclusions

In summary, 2-benzylamino and 2-arylaminoimidazolines were prepared by C-2 amination *via* the corresponding 2-chlorodihydroimidazoles or 2-methylsulfanyldihydroimidazoles, respectively. The first procedure is the method of choice when primary amines, such as benzylamines, are employed and also allows the preparation of bis(dihydroimidazole)amino derivatives by choosing the adequate experimental conditions. On the other hand, the use of *N*-acyl-2-methylsulfanyldihydroimidazoles allows the reactions with aromatic amines, such as *p*-anisidine, to be carried out, though it requires protection of imidazole nitrogen atom as its acetyl derivative. Finally, palladium catalyzed Buchwald-Hartwig amination allows the C-N coupling between 2-haloimidazoles and aromatic amines.

Experimental Section

General experimental methods. Melting points were determined in unsealed capillary tubes. IR spectra were obtained on KBr pellets (solids) or in film over NaCl pellets (oils). NMR spectra were recorded at 20–25 ºC, running at 300 or 500 MHz for ^{1}H and 75.5 or 125.7 MHz for ^{13}C in $CDCl_3$ solutions, unless stated otherwise. Assignment of individual ^{13}C and ^{1}H resonances is supported by DEPT experiments and 2D experiments (COSY, HMBC, HSQC, NOESY) when necessary. Mass spectra were recorded under electron impact at 70 eV. Exact mass was obtained using a TOF detector. GC-MS analyses were performed using a TRB-1 column (methyl polysiloxane, 30 m × 0.25 mm × 0.25 μm). TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography on silica gel was performed with Kieselgel 60 (230-400 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 ºC) and purged with argon.

1-Acetylimidazolidin-2-one (**1b**).[41] A solution of imidazolidin-2-one **1a** (0.47 g, 5.3 mmol) in Ac_2O (4.5 mL) was refluxed for 30 min. The reaction mixture was allowed to cool down to room temperature, and a white precipitate was formed. The precipitate was collected by vacuum filtration, and the filtrate was concentrated *in vacuo*. The combined solids obtained were purified by flash column chromatography (silicagel, AcOEt) to obtain **1b**, as a white solid (0.43 g, 63%) mp (EtOH) 180-181 ºC (Lit.[41] 177-178 ºC); IR (KBr): ν_{max} 1654, 1725, 3259 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.47 (s, 3H), 3.47 (t, *J* 8.1 Hz, 2H), 3.92 (t, *J* 8.1 Hz, 2H), 5.87 (broad s, 1H); ^{13}C NMR (75.5 MHz) δ 23.3, 36.4, 42.1, 157.2, 170.8; MS (CI, 230 eV) *m/z* (%) 129 [MH^+], 128 [M^+], 85 (100), 70 (10).

2-Chloro-4,5-dihydro-1*H*-imidazole (2a). To a solution of imidazolidin-2-one **1a** (1.61 g, 18.35 mmol) in dry CH_3CN (40 mL), PCl_5 (5.80 g, 27.52 mmol) was added dropwise along 10 minutes at room temperature, and the resulting mixture was stirred at this temperature for 3 days, and organic solvent was removed *in vacuo*. Trituration with acetone (40 mL) afforded 2-chlorodihydroimidazole (**2a**) (1.06 g, 55 %) as a brown solid, which proved to be highly hygroscopic: IR (KBr): ν_{max} 1725, 3237 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 3.28 (t, *J* 7.9 Hz, 2H), 3.70 (t, *J* 7.9 Hz, 2H), 11.8 (broad s, 1H); ^{13}C NMR (75.5 MHz, DMSO-*d*$_6$) δ 39.2, 44.7, 160.2. HRMS (EI, 70 eV) Calcd. for $C_3H_5ClN_2$: 104.0141; found: 104.0218. Data have been reported for the hydrochloride.[39]

***N*-(Imidazolidin-2-ylidene)benzylamine (3).** To a solution of 2-chlorodihydroimidazole **2a** (0.85 g, 8.10 mmol) in dry CH_2Cl_2 (30 mL), benzylamine (0.89 mL, 8.10 mmol) was added at room temperature. After stirring the mixture at this temperature for 19 h, Et_2O (100 mL) was added to give a brown solid. This solid was solved in H_2O (20 mL) and 10 % NaOH was added until pH 10. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford **3** (0.88 g, 62 %) as an oil: IR (film): ν_{max} 1666 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.27 (s, 2H), 3.87 (s, 4H), 4.49 (s, 2H) 7.25–7.37

(m, 5H). ^{13}C NMR (75.5 MHz) δ 29.7, 53.4 , 127.0, 128.2, 128.8, 143.4, 162.0. HRMS (EI, 70 eV) Calcd. for $C_{10}H_{13}N_3$: 175.1109; found: 175.1109.

***N*-benzyl-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-4,5-dihydro-1*H*-imidazol-2-amine (4).** To a solution of 2-chlorodihydroimidazole **2a** (0.93 g, 8.92 mmol) in dry CH_2Cl_2 (30 mL), benzylamine (0.48 mL, 4.46 mmol) was added at room temperature, and the reaction mixture was refluxed for 21 h. The mixture was allowed to cool down to room temperature and then precipitated by addition of Et_2O (100 mL). The precipitate was collected by vacuum filtration, and the brown solid was dissolved in H_2O (20 mL) and 10 % NaOH was added until pH 10. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford **4** (0.64 g, 60 %) as an oil: IR (film): ν_{max} 1655 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.12 (broad s, 2H), 3.85 (s, 8H), 4.49 (s, 2H) 7.23–7.38 (m, 5H). ^{13}C NMR (75.5 MHz) δ 46.3, 53.3, 126.6, 127.0, 127.7, 128.4, 143.2. HRMS (EI, 70 eV) Calcd. for $C_{13}H_{17}N_5$: 243.1484; found: 243.1474.

2-(Methylthio)-4,5-dihydro-1*H*-imidazol-1-ium iodide (6·HI).[48] To a solution of imidazolidine-2-thione **5** (9.82 g, 94.2 mmol) in dry MeOH (20 mL), methyl iodide (14.70 g, 103.59 mmol) was added at room temperature, and the resulting mixture was refluxed for 2 h. The reaction mixture was allowed to cool down to room temperature to give a white solid precipitate. Et_2O (20 mL) was added, and the solid was collected by vacuum filtration. The solid was crystallized from MeOH to afford the dihydroimidazol-2-thione **6**·HI (21.77 g, 95 %) as a white solid: mp (MeOH) 143–144 ºC (Lit.[42] 142 ºC); IR (KBr): ν_{max} 1555, 3131 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.63 (s, 3H), 3.86 (s, 4H), 9.96 (broad s, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.6, 45.1, 170.4; MS (CI, 230 eV) *m/z* (%) 117 (MH^+, 6), 116 (M^+, 100), 87 (43), 83 (41), 74 (19), 72 (93), 59 (18).

Synthesis of *N*-acyldihydroimidazoles 7a-c. General procedure: To a solution of **6** (1 mmol) in $ClCH_2CH_2Cl$ (20 mL), was added Et_3N (0.5 mmol). The mixture was cooled to 0 ºC and the acylating agent (1.3 mmol) was added. The resulting mixture was stirred at room temperature for 2 h, and organic solvent was removed *in vacuo*. Purification by flash column chromatography (silicagel) afforded the corresponding *N*-acylimidazoles **7a-c**.

1-Acetyl-2-(methylthio)-4,5-dihydro-1*H*-imidazole (**7a**).[29] According to the general procedure, dihydroimidazole **6** (2.08 g, 8.51 mmol) was treated with Et_3N (0.64 mL, 4.60 mmol) and Ac_2O (1.12 mL, 11.50 mmol). Purification by flash column chromatography (silicagel, AcOEt : MeOH 20 %) afforded *N*-acetyldihydroimidazole **7a** (1.21 g, 90 %) as a white solid: mp (AcOEt) 55–57 ºC; IR (KBr): ν_{max} 1578, 1672 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.08 (s, 3H), 2.26 (s, 3H), 3.77–3.83 (m, 2H), 3.92–3.99 (m, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 14.7, 24.0, 47.7, 53.7, 158.5, 167.7; MS (CI, 230 eV) *m/z* (%) 159 (MH^+, 2), 158 (M^+, 8), 143 (100), 115 (26), 87 (29), 85 (43), 83 (52), 71 (70), 57 (81). HRMS (EI, 70 eV) Calcd. for $C_6H_{10}N_2OS$: 158.0514; found: 158.0513.

1-Methoxycarbonyl-2-(methylthio)-4,5-dihydro-1*H*-imidazole (**7b**).[49] According to the general procedure, dihydroimidazole **6** (0.25 g, 1.02 mmol) was treated with Et_3N (0.08 mL, 0.55 mmol) and methyl chloroformate (0.11 mL, 1.38 mmol). Purification by flash column

chromatography (silicagel, AcOEt), afforded *N*-methoxycarbonyldihydroimidazole **7b** (0.16 g, 90 %) as a white solid: mp (AcOEt) 105–107 ºC (Lit.[49] 103–105 ºC); IR (KBr): ν_{max} 1584, 1713 cm^{-1}; ^1H NMR (300 MHz) δ 2.42 (s, 3H), 3.80 (s, 3H), 3.88–3.91 (m, 4H). ^{13}C NMR (75.5 MHz) δ 15.0, 47.3, 53.1, 53.8, 152.3, 159.5; MS (CI 230, eV,) *m/z* (%) 175 (MH^+ 9), 174 (M^+, 100), 115 (66), 87 (26), 72 (41), 70 (23).

1-(Benzyloxycarbonyl)-2-(methylthio)-4,5-dihydro-1*H*-imidazole (**7c**).[50] According to the general procedure, dihydroimidazole **6** (0.27 g, 1.13 mmol) was treated with Et_3N (0.09 mL, 0.61 mmol) and benzyl chloroformate (0.23 mL, 1.52 mmol). Purification by flash column chromatography (silicagel, 10% AcOEt/hexane) afforded *N*-benzyloxycarbonyldihydroimidazole **7c** (0.16 g, 90 %) as a white solid: mp (AcOEt) 67–69 ºC [Lit.[50] mp (AcOEt) 61 ºC]; IR (KBr): ν_{max} 1578, 1713 cm^{-1}; ^1H NMR (300 MHz) δ 2.41 (s, 3H), 3.89 (s, 4H), 5.20 (s, 2H), 7.34–7.38 (m, 5H); ^{13}C NMR (75.5 MHz) δ 15.0, 47.4, 53.7, 67.8, 128.3, 128.4, 128.6, 135.5, 151.7, 159.5. MS (70 eV, EI) *m/z* (%) 250 (M^+, 15), 191 (11), 91 (100).

1-(2-(4-methoxyphenylamino)-4,5-dihydro-1*H*-imidazol-1-yl)ethanone (8). A mixture of **7a** (0.10 g, 0.63 mmol) and *p*-anisidine (0.08 g, 0.63 mmol) in AcOH (0.5 mL)/EtOH (4.5 mL) was heated at reflux for 24 h. The organic solvent was removed *in vacuo*, afforded **8** (0.06 g, 40 %) as an oil: IR (film): ν_{max} 1666 cm^{-1}; ^1H NMR (300 MHz) δ 1.96 (s, 3H), 3.68 (broad s, 5H), 3.77 (s, 3H) 6.84 (d, *J* 8.9 Hz, 2H), 7.10 (d, *J* 8.9 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 23.8, 43.0, 55.5, 114.9, 125.4, 129.2, 158.1, 160.0, 178.9; MS (70 eV, EI) *m/z* (%) 233 (M^+, < 1), 191 (41), 176 (100), 134 (37), 122 (54), 69 (31). HRMS (EI, 70 eV) Calcd. for $C_{12}H_{15}N_3O_2$: 233.1164; found: 233.1165.

***N*-(4-Methoxyphenyl)-1-methyl-1*H*-imidazol-2-amine** (**10**). To a solution of 2-bromo-1-methyl-1*H*-imidazole (**9**) (0.10 g, 0.60 mmol) in dry toluene (6 mL), *p*-anisidine (0.15 g, 1.19 mmol), $Pd_2(dba)_3$ (51.02 mg, 0.06 mmol), BINAP (0.11 g, 0.18 mmol) and Cs_2CO_3 (0.39 g, 1.19 mmol) were added sequentially, and the resulting mixture was heated at 100 ºC for 21 h. The reaction was quenched by the addition of saturated $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous phase was extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*, to obtain **10** (0.11 g, 90 %) as an oil. This product was unstable and could not be further purified by column chromatography: IR (film): ν_{max} 3343 cm^{-1}; ^1H NMR (300 MHz) δ 3.44 (broad s, 1H), 3.55 (s, 3H), 3.70 (s, 3H), 6.67 (d, *J* 9.0 Hz, 2H), 6.72 (d, *J* 9.0 Hz, 2H), 6.92 (d, *J* 1.4 Hz, 1H), 6.97 (d, *J* 1.4 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 34.3, 55.5, 114.6, 116.1, 119.8, 122.8, 129.5, 139.9, 152.5.

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