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-methylsulanyldihydroimidazoles 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-aminimidazoles of the oroidin family and their synthetic analogs⁴,⁵ possess anti-biofilm activities,⁶,⁷ while 2-arylamino or iminoimidazolidines (e.g. clonidine), known hypertensive
agents,8 have also been evaluated as \(\alpha_2\)-adrenoceptor antagonists for the treatment of depression (Figure 1). 9-11

![Figure 1](image_url)

**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 guanidines12,13 or 2-aminopyrimidines (protected guanidines)14 to \(\alpha\)-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 cyanoamide and \(\alpha\)-aminoketones16 or \(\alpha\)-aminoesters.6 In a similar way, the corresponding 2-aminoimidazolines have been synthesized by condensation of \(N\)-arylcyanimidodithioates 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 kealiquinone.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-sulfonate32 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, \(X = \text{Cl}\)), or 2-methylsulfanyldihydroimidazoles (I,
X = SCH₃, 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).

\[
\begin{align*}
\text{I} & \quad X = \text{Cl, SCH₃, Br} \\
& \quad R^1 = \text{H, OAc, CH₃} \\
\text{II} & \quad \text{R}^2\text{NH}_2 \quad \text{NHR}^2 \\
\text{III} & \quad R^1 \quad R^2 \quad R^1 \\
\end{align*}
\]

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. 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. 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 = SCH₃) 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 POCl₃ only led to low to moderate yields (22-74%) of the N-acetylated imino derivatives.

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 POCl₃ 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 and has been prepared mainly by chlorination of imidazolidine-2-thione. 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-aminoimidazolines) 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-acetyl-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-methylsulfonyldihydroimidazole 6 by treatment with methyl iodide in methanol under reflux (Scheme 2). Compound 6 was easily acylated with Ac₂O, ClCO₂CH₃, or ClCO₂Bn 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-methylsulfonyldihydroimidazole 6 with various primary alkyl amines has been reported, no reaction was obtained when 6 was treated with benzylamine or p-anisidine. Thus, the use of methylsulfonyl 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 13C 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.

Our next step was to replace the imidazolidine-amine unit by a 2-aminoimidazole. As stated above, introduction of the NH₂ 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. 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 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, while a series of amide substituted purine derivatives were synthesized via palladium-catalyzed amidation reactions. 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).

\[
\begin{align*}
\text{Br} & \quad \text{N} \quad \text{CH}_3 \\
9 & \quad \text{H}_2\text{N} \quad \text{OMe} \\
\text{Pd(dba)}_2 (10 \text{ mol\%}) & \quad \text{BINAP, Cs}_2\text{CO}_3 \\
& \quad \text{toluene, 100 °C, 21 h} \\
\text{N} \quad \text{CH}_3 & \quad \text{N} \quad \text{H} \\
\text{OMe} & \quad 10 (90 \%) \quad (\text{Scheme 3})
\end{align*}
\]

**Scheme 3**

Initial efforts to effect this palladium-catalyzed reaction employed the protocol developed by the Rizzo group\(^4\) for the coupling of related substrates, 8-bromodeoxyguanosine derivatives: \( \text{Pd}_2(\text{dba})_3 \) (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-aminimidazole 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 \( \text{Cs}_2\text{CO}_3 \), the C-N coupling product, \( N \)-aryl-1-methyl-1H-imidazole-2-amine (10), was obtained in very good crude yield (90\%), based on \(^1\text{H} \) 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 \( \delta = 139.9 \) ppm in \(^{13}\text{C} \) NMR, while the aromatic protons meta and ortho appear at \( \delta 6.67, (d, J 9.0 \text{ Hz}) \) and \( \delta 6.72, (d, J 9.0 \text{ Hz}) \), respectively.\(^3\) 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 1H and 75.5 or 125.7 MHz for 13C in CDCl₃ solutions, unless stated otherwise. Assignment of individual 13C and 1H 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). A solution of imidazolidin-2-one 1a (0.47 g, 5.3 mmol) in Ac₂O (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. 177-178 ºC); IR (KBr): νmax 1654, 1725, 3259 cm⁻¹; 1H 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); 13C 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-1H-imidazole (2a). To a solution of imidazolidin-2-one 1a (1.61 g, 18.35 mmol) in dry CH₃CN (40 mL), PCl₅ (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): νmax 1725, 3237 cm⁻¹; 1H NMR (300 MHz, DMSO-d₆) δ 3.28 (t, J 7.9 Hz, 2H), 3.70 (t, J 7.9 Hz, 2H), 11.8 (broad s, 1H); 13C NMR (75.5 MHz, DMSO-d₆) δ 23.3, 36.4, 42.1, 157.2, 170.8; MS (Cl, 230 eV) m/z (%) 129 [MH⁺], 128 [M⁺], 85 (100), 70 (10).

N-(Imidazolidin-2-ylidene)benzylamine (3). To a solution of 2-chlorodihydroimidazole 2a (0.85 g, 8.10 mmol) in dry CH₂Cl₂ (30 mL), benzylamine (0.89 mL, 8.10 mmol) was added at room temperature. After stirring the mixture at this temperature for 19 h, Et₂O (100 mL) was added to give a brown solid. This solid was washed in H₂O (20 mL) and 10 % NaOH was added until pH 10. The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to afford 3 (0.88 g, 62 %) as an oil: IR (film): νmax 1666 cm⁻¹; 1H NMR (300 MHz) δ 1.27 (s, 2H), 3.87 (s, 4H), 4.49 (s, 2H) 7.25–7.37
4\text{mmol}) and methyl chloroformate (0.11 mL, 1.38 mmol). Purification by flash column chromatography (silicagel, AcOEt : MeOH (3 \times 20 \text{mL})]. The combined organic extracts were dried (Na\text{2SO}_4) and concentrated in \textit{vacuo} to afford 4 (0.64 g, 60 \%) as an oil: IR (film): ν\textit{max} 1655 \text{cm}^{-1}; ^1\text{H} \text{NMR (300 MHz)} δ 2.12 (broad s, 2H), 3.85 (s, 8H), 4.49 (s, 2H) 7.23–7.38 (m, 5H). \textsuperscript{13}\text{C} \text{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\textsubscript{11}H\textsubscript{16}N\textsubscript{5}: 243.1484; found: 243.1474.

2-(Methylthio)-4,5-dihydro-1\textit{H}-imidazol-1-ium iodide (6•HI).

According to the general procedure, dihydroimidazole 6 (2.08 g, 8.51 mmol) was treated with Et\textsubscript{3}N (0.64 mL, 4.60 mmol) and Ac\textsubscript{2}O (1.12 mL, 11.50 mmol). Purification by flash column chromatography (silicagel, AcOEt : MeOH 20 \%) afforded N-acetylthioidihydroimidazole 7a (1.21 g, 90 \%) as a white solid: mp (AcOEt) 55–57 \degree\text{C}; IR (KBr): ν\textit{max} 1578, 1672 \text{cm}^{-1}; ^1\text{H} \text{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\text{C} \text{NMR (75.5 MHz, DMSO-}d_6) δ 14.7, 24.0, 47.7, 53.7, 158.5, 167.7; MS (Cl, 230 eV) m/z (%) 159 (MH\textsuperscript{+}, 2), 158 (M\textsuperscript{+}, 8), 143 (100), 115 (26), 87 (29), 85 (43), 83 (52), 71 (70), 57 (81). HRMS (EI, 70 eV) Calcd. for C\textsubscript{6}H\textsubscript{10}N\textsubscript{2}OS: 158.0514; found: 158.0513.

1-Methoxycarbonyl-2-(methylthio)-4,5-dihydro-1\textit{H}-imidazole (7b).

According to the general procedure, dihydroimidazole 6 (0.25 g, 1.02 mmol) was treated with Et\textsubscript{3}N (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 °C (Lit.\(^49\) 103–105 °C); IR (KBr): \(v_{\text{max}}\) 1584, 1713 cm\(^{-1}\); \(^1\)H NMR (300 MHz) \(\delta\) 2.42 (s, 3H), 3.80 (s, 3H), 3.88–3.91 (m, 4H). \(^{13}\)C NMR (75.5 MHz) \(\delta\) 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-(Benzzyloxycarbonyl)-2-(methylthio)-4,5-dihydro-1H-imidazole (7c).\(^{50}\) According to the general procedure, dihydroimidazole 6 (0.27 g, 1.13 mmol) was treated with Et\(_3\)N (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): \(v_{\text{max}}\) 1578, 1713 cm\(^{-1}\); \(^1\)H NMR (300 MHz) \(\delta\) 2.41 (s, 3H), 3.89 (s, 4H), 5.20 (s, 2H), 7.34–7.38 (m, 5H); \(^{13}\)C NMR (75.5 MHz) \(\delta\) 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-1H-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): \(v_{\text{max}}\) 1666 cm\(^{-1}\); \(^1\)H NMR (300 MHz) \(\delta\) 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) \(\delta\) 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\(_3\)O\(_2\): 233.1164; found: 233.1165.

\(N\)-(4-Methoxyphenyl)-1-methyl-1H-imidazol-2-amine (10). To a solution of 2-bromo-1-methyl-1H-imidazole (9) (0.10 g, 0.60 mmol) in dry toluene (6 mL), \(p\)-anisidine (0.08 g, 0.63 mmol), Pd\(_2\)(dba)\(_3\) (51.02 mg, 0.06 mmol), BINAP (0.11 g, 0.18 mmol) and Cs\(_2\)CO\(_3\) (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\(_2\)SO\(_4\)) 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): \(v_{\text{max}}\) 3343 cm\(^{-1}\); \(^1\)H NMR (300 MHz) \(\delta\) 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) \(\delta\) 34.3, 55.5, 114.6, 116.1, 119.8, 122.8, 129.5, 139.9, 152.5.

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