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Short Note

5-(4-Chlorophenyl)-*N*,1-di-*o*-tolyl-1*H*-imidazole-2-amine

Francesco Messa [1], Paride Papadia [1], Serena Perrone [1,*] and Antonio Salomone [2,*]

[1] Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, Università del Salento, Prov.le Lecce-Monteroni, 73100 Lecce, Italy
[2] Dipartimento di Chimica, Università degli Studi di Bari "Aldo Moro", Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, 70125 Bari, Italy
* Correspondence: serena.perrone@unisalento.it (S.P.); antonio.salomone@uniba.it (A.S.)

Abstract: A new 2-amino imidazole derivative, 5-(4-chlorophenyl)-*N*,1-di-o-tolyl-1H-imidazole-2-amine (**3**), has been synthesized using a green approach. The reaction was conducted in a ChCl (cholinium chloride)/urea eutectic mixture, which is a nature-inspired and environmentally friendly reaction medium. The proposed reaction mechanism involves the preliminary regioselective alkylation of the N_{sp2} of guanidine (**2**), followed by an intramolecular condensation between the carbonyl moiety and the secondary N'_{sp3}. Finally, a tautomerization/aromatization step furnished the final product (**3**). Notably, 2-amino imidazole (**3**) could be isolated in high yield (91%), just by filtration from the DES/water mixture and subsequent crystallization; the remaining ChCl/urea could be recycled, after water removal, for four consecutive reactions without any significant drop in the (**3**) yield. The product has been fully characterized by ^{1}H, ^{13}C, 2D ^{1}H-^{13}C HSQC, and 2D ^{1}H-^{13}C HMBC NMR; FT-IR spectroscopy; and EI-MS spectrometry.

Keywords: 2-aminoimidazole; α-chloroketone; *N*,*N*′-diarylguanidine; deep eutectic solvent; solvent recycle; sustainable synthesis

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1. Introduction

2-Aminoimidazole (2-AI) derivatives are a valuable class of nitrogen-containing five-membered heterocycles with wide relevance both in the chemical and pharmaceutical fields. Indeed, this heterocyclic core has been extensively employed in coordination chemistry [1,2] and in organocatalysis [3]. Moreover, the 2-AI ring proved to be an important pharmacophore in medicinal chemistry, especially in the synthesis of small bioactive molecules, since it acts as a bioisostere of guanidine, triazoles and benzamidine [4]. For these reasons, 2-AI scaffold represents a key structural element in a wide range of FDA-approved drugs, such as emedastine [5] and astemizole [6], acting as antagonists of H1 histamine receptor (Figure 1a), the anthelmintics albendazole [7] and mebendazole [8] (Figure 1b), and linagliptin, which is an inhibitor of dipeptidyl peptidase (DPP)-4 used for the treatment of type 2 diabetes mellitus [9] (Figure 1c).

The classic synthetic methods for 2-aminoimidazoles include several categories of chemical transformations, such as condensation reactions, nucleophilic substitutions, coupling reactions, ring transformations [10,11], and metal-mediated cyclization reactions [12,13]. Despite the great variety of strategies present in the literature, the preparation of 2-aminoimidazoles is often performed in volatile organic solvents (VOCs) as reaction media (e.g., dioxane, DMF, DMSO, toluene), and generally requires an inert atmosphere with strict exclusion of humidity [10,11]. These features make these synthetic procedures unsuitable for industrial applications.

Over the past decades, sustainability has become an imperative issue that has prompted both academic and industrial scientists to develop more environmentally beneficial and atom-efficient chemical processes. Indeed, in heterocycle synthesis, the use of deep eutectic

solvents (DESs) as a green and sustainable alternative to toxic and hazardous VOCs is recently gaining great interest [14].

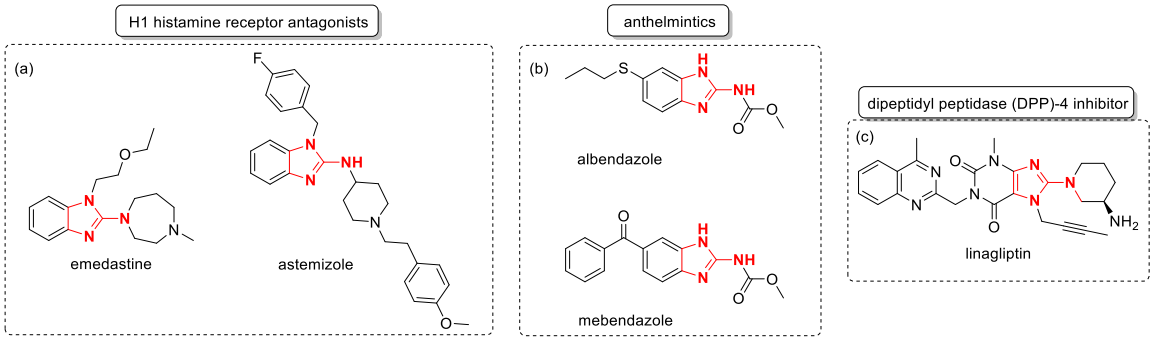


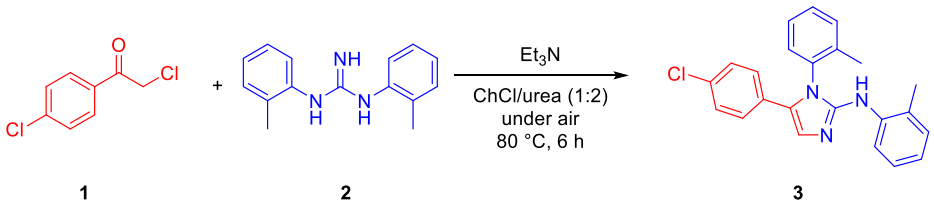
Figure 1. Examples of FDA-approved bioactive molecules containing 2-aminoimidazole motif (in red). (**a**) histamine receptor antagonists; (**b**) anthelmintics drugs; (**c**) DPP-4 inhibitor for the treatment of type 2 diabetes mellitus.

DESs are defined as a mixture of at least two components that are capable of forming an eutectic mixture with a melting point far below that of each component [15]. Nowadays, DESs are classified, based on their composition, into five typologies. The best choice, based on environmental sustainability and low toxicity, is certainly type III DES [16]. They are formed by hydrogen bond acceptors (HBA, e.g., quaternary ammonium salts) and hydrogen bond donors (HBD) in different molar ratios. The components of type III DESs are usually bio-inspired molecules derived from renewable feedstocks, such as cholinium chloride (ChCl), urea and derivatives, polyols like glycerol, carbohydrates like glucose or sucrose, carboxylic acids like acetic acid, or fatty acids [17].

In accordance with our research interests, focused on the development of sustainable synthetic methodologies [18–23], in this manuscript we report the preparation of the novel 5-(4-chlorophenyl)-N,1-di-o-tolyl-1H-imidazole-2-amine (**3**) in a ChCl/urea eutectic mixture as a sustainable reaction medium. The reported methodology is characterized by green and eco-friendly conditions as it employed a bio-inspired and easily recyclable DES, mild reaction settings (under air, 80 °C), and metal-free conditions. Moreover, it is important to mention that the separation of 2-AI **3** was accomplished through a straightforward filtration process from the reaction mixture, followed by crystallization, which eliminates the need for environmentally harmful column chromatography purification.

2. Results and Discussion

2-AI, namely 5-(4-chlorophenyl)-N,1-di-o-tolyl-1H-imidazole-2-amine (**3**) was prepared via a condensation reaction between the α-chloroketone 2-chloro-1-(4-chlorophenyl) ethan-1-one (**1**, 1.0 mmol) and a moderate excess (1.3 equiv.) of 1,3-di-*o*-tolylguanidine (**2**), in ChCl/urea (1:2 mol/mol) as the green medium, using Et_3N as the base, under mild reaction condition and short reaction time (under air, 80 °C, 6 h, Scheme 1) [24]. We were delighted to observe that, upon completion of the reaction and cooling of the mixture to room temperature, the DES mixture yielded the product 2-AI 3 in the form of a precipitate. The isolation of 2-AI 3 was a straightforward process, as it could be obtained with high yield (91%) and purity (95%, determined via ^{1}H NMR analysis using dimethyl sulfone as an internal standard) by simply adding water to the reaction mixture and filtering the resulting precipitate through paper. The ChCl/urea eutectic mixture, which exhibits both an ionic and protic nature, facilitates the dissolution of polar starting materials and the subsequent precipitation of the less polar product **3**. This unique property of the DES eliminates the need for conventional purification techniques, such as liquid–liquid extraction and column chromatography, which typically rely on the use of toxic and volatile organic compounds (VOCs).



Scheme 1. Synthesis of the 2-AI derivative 5-(4-chlorophenyl)-1,2-di-*o*-tolyl-*1H*-imidazole **3** from α-chloroketone **1** and *N,N′*-diarylguanidine **2** in ChCl/urea as DES.

Moreover, the purity of 2-AI **3** can be raised up to >98% after a crystallization process employing Et_2O as the solvent and petroleum ether (PE) as the non-solvent (Et_2O/PE = 8:2 *v*/*v*).

Notably, after the recovery of product **3** by filtration, the DES medium proved to be easily recyclable: following water removal from the eutectic mixture by a rotary evaporator and the addition of fresh reagents (α-chloroketone **1,** guanidine **2**, and Et_3N), the eutectic mixture was reused for an additional four reaction cycles without any significant drop in the yield of **3** (Figure 2).

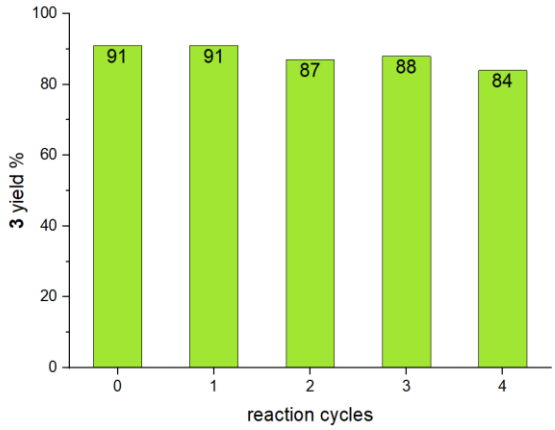
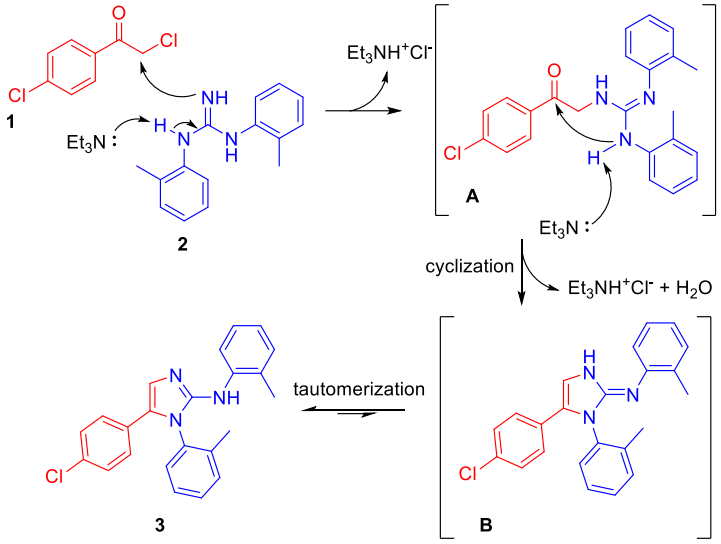


Figure 2. Yield of 2-AI derivative **3** over four successive reaction cycles.

Regarding the reaction mechanism, we hypothesize the following pathway. At first, the nucleophilic substitution mediated by the 3-di-*o*-tolylguanidine (**2**) to the α-chloroketone (**1**) affords the intermediate adduct **A**, which can, subsequently, undergo an intramolecular nucleophilic attack of the *o*-tolyl substituted nitrogen on the carbonyl group to generate, after a dehydration process, intermediate **B**. The latter generates the 2-AI derivative **3** after tautomerization (Scheme 2).

It should be noted that the ChCl/urea eutectic mixture, besides improving the reaction sustainability (by replacing the common VOCs and avoiding chromatographic procedures), could be responsible for the shortening of the reaction time (6 h) compared to the same process carried out in THF or DMF as reaction media (12–24 h) [24,25]. Particularly, hydrogen bond catalysis, mediated by DES components (ChCl and urea), could activate reagents and intermediates, both improving the electrophilicity of the α-chloroketone carbonyl group and exalting the nitrogen nucleophilicity of guanidine **2**.

2-AI derivative 5-(4-chlorophenyl)-1,2-di-*o*-tolyl-*1H*-imidazole **3** was fully characterized by various spectroscopic techniques (^{1}H, ^{13}C, 2D ^{1}H-^{13}C HSQC, and 2D ^{1}H-^{13}C HMBC NMR, and FT-IR) and GC-MS spectrometry (see Supplementary Materials for copies of spectra).



Scheme 2. Proposed reaction mechanism for the synthesis of 2-AI **3** in ChCl/urea DES.

The ^{1}H NMR spectrum of 2-AI **3**, recorded at 25 °C in $CDCl_3$ solution, exhibits two characteristic singlet protons at 7.03 ppm due to the proton bonded to the C-4 of the imidazole ring and the broad singlet at 5.68 ppm belonging to the nitrogen of the secondary aminic group, which is consistent with the chemical shift reported for similar 2-AI derivatives in previous work [24]. The singlet signals at 2.20 and 1.94 ppm were clearly attributed to the methyl protons of the *o*-tolyl moiety. Finally, six multiplets are shown in the range from 8.33 to 6.85 ppm, corresponding to the 12 H of the aromatic substituents (Figure 3, see Supplementary Materials for a copy of the ^{1}H NMR spectrum).

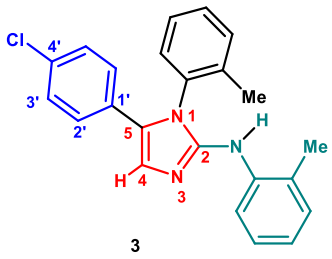


Figure 3. Structure of 2-AI derivative **3** with selected atoms labeled.

The ^{13}C NMR spectrum shows the presence of three characteristic signals belonging to the carbons of the imidazole ring: (1) the most electron-poor carbon C-2 resonates at 144.6 ppm, as confirmed by the cross-peak with proton H-4 at 6.91 ppm observed in the HMBC spectrum; (2) the C-4 carbon resonates at 111.7 ppm and couples with proton H-4, as shown in the HSQC spectrum; and (3) the peak at 137.16 ppm is due to the resonance of the quaternary carbon C-5, which, in the HMBC spectrum, couples with protons H-4 of the imidazole ring and H-2′ of the 4-chlorophenyl substituent. All remaining cross-peaks observed in 2D-HSQC and 2D-HMBC are in accordance with the structure of 2-aminoimidazole derivative **3** (see Supplementary Materials for copies of ^{13}C NMR, 2D HSQC, and 2D HMBC spectra).

3. Materials and Methods

3.1. General Methods

1D and 2D NMR spectra were acquired on a Bruker Avance III 400 instrument, operating at 400.12 MHz ^{1}H resonance frequency, equipped with an inverse dual resonance broad band probe. Chemical shifts are reported in parts per million (δ). The following abbreviations have been used to explain the multiplicities: s = singlet, m = multiplet,

br = broad. FT-IR spectrum was recorded on a Perkin-Elmer 681 spectrometer. GC-MS analysis was performed on the HP 5995C model. Reagents and solvents, unless otherwise specified, were purchased from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA) and used without any further purification. Petroleum ether refers to the 40–60 °C boiling fraction. The DES ChCl/urea (1:2 mol/mol) was prepared by heating the corresponding individual components at 80 °C while stirring for 30 min until a clear eutectic mixture was obtained.

3.2. Synthesis of 5-(4-Chlorophenyl)-1,2-di-o-tolyl-1H-imidazole (3)

In a 10 mL round bottom flask, 2-chloro-1-(4-chlorophenyl)ethan-1-one **1** (1.0 mmol, 189 mg), 1,3-di-*o*-tolylguanidine **2** (1.3 mmol, 311 mg) and Et_3N (1.0 mmol, 101.2 mg, 139 µL) were sequentially added to the ChCl/urea eutectic mixture (2.0 mL). The mixture was then heated to 80 °C for 6 h under vigorous magnetic stirring until α-chloroketone **1** disappeared, as revealed by GC-MS analysis. After this time, the reaction mixture was cooled to room temperature, and H_2O (2.0 mL) was added. The purification of product 2-AI **3** was achieved by filtration on paper. The yellow solid obtained was further purified by crystallization from Et_2O/PE (ca. 8/2 *v*/*v* ratio) affording the pure product in 91% yield (339 mg) as a pale yellow solid with m.p. = 125–127 °C.

^{1}H NMR (400.12 MHz, $CDCl_3$): δ 8.33–8.31 (m, 1H), 7.80–7.77 (m, 2H), 7.45–7.32 (m,6H), 7.26–7.22 (m, 1H), 7.07–7.04 (m, 1H), 7.03 (s, 1H), 6.89–6.85 (m, 1H), 5.68 (br s, 1H, NH), 2.20 (s, 3H), 1.94 (s, 3H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 144.7, 138.8, 137.3, 136.1, 134.6, 132.9, 131.9, 131.8, 130.1, 129.9, 128.6, 127.9, 127.5, 127.2, 125.8, 123.8, 121.2, 116.7, 111.9, 17.6, 17.1 ppm. FT-IR (KBr, cm^{-1}): 3434, 3131, 3062, 2976, 2925, 2856, 1901, 1686, 1593, 1539, 1484, 1464, 1405, 1378, 1331, 1291, 1254, 1178, 1092, 1012, 944, 908, 879, 835, 736, 699. GC-MS (70 eV) m/z: 375 (M^++2, 25), 373 (M+, 66), 358 (9), 267 (100), 204 (9), 118 (15), 91 (21), 65 (16).

4. Conclusions

The novel 2-AI derivative 5-(4-chlorophenyl)-1,2-di-*o*-tolyl-*1H*-imidazole **3** was smoothly prepared via the reaction between α-chloroketone **1** and the guanidine derivative **2** in the bio-inspired and easily recyclable eutectic mixture ChCl/urea. Compound **3** was isolated in 91% yield simply by a filtration process followed by crystallization and fully characterized by ^{1}H, ^{13}C, 2D ^{1}H-^{13}C HSQC, and 2D ^{1}H-^{13}C HMBC NMR; FT-IR spectroscopy; and GC-MS spectrometry.

Supplementary Materials: The following spectra can be downloaded online: ^{1}H-NMR ($CDCl_3$, 400.13 MHz), ^{13}C-NMR ($CDCl_3$, 100.26 MHz), 2D ^{1}H-^{13}C HSQC NMR ($CDCl_3$), 2D ^{1}H-^{13}C HMBC NMR ($CDCl_3$), FT-IR (KBr), EI-MS (70 eV).

Author Contributions: A.S. and S.P. designed chemical synthesis, analyzed results, and wrote the manuscript. F.M. performed the experiments, analyzed results, and wrote the manuscript. P.P. performed the NMR experiments, analyzed results, and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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