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Attractive and simple synthesis route from benzil to two different types of amino acid-derived imidazoles: first preliminary results

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Binding imidazoles to amino acids is an interesting synthetic challenge due to the structural particularities of each one. This research found an attractive and simple (almost green) synthesis route to develop two types of imidazoles anchored to amino acids valine and phenylalanine. FT-IR and 1HNMR support this synthetic route.

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Imidazoles are heterocyclic compounds that have known biological activity for many years.[1] Their activity is highly diverse, ranging from antifungal to antibacterial. This important heterocycle nucleus can be found in many drugs, such as metronidazole, nimorazole, clotrimazole, miconazole, methimazole, losartan, nizofenone, azathioprine, pilocarpine, *etc.*[2–13]

Some of these structures contain substituents at position 2 of the imidazole ring as well as position 1, where the hydrogen on the pyrrolic nitrogen is replaced (Fig. 1). Imidazole is a ring present in the body through the amino acid histidine, and some natural bioactive compounds are formed from other amino acids, with numerous examples in the literature.[14] Although studies on imidazoles derived from amino acids have been described, they were focused on the synthesis of imidazole-carboxylate compounds with a simple structure.[15] In a way, these facts could be an inspiration for the rational design of potential drugs or bioactive compounds containing both molecular fragments, amino acids and imidazoles, considering that current drug design barely includes any type of amino acid in their structures.[16] This observation motivated our research with the aim of incorporating amino acids into the imidazole nucleus, seeking to obtain equal or better biological activities than those described previously for our team.[17,18] Specifically, the proposed molecules of this paper have been previously studied as potential inhibitors of NS3 and NS5 dengue virus proteins.[19]

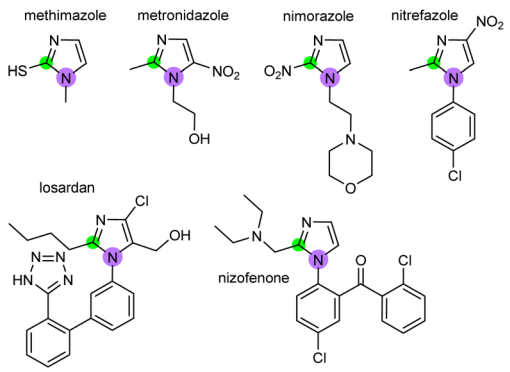

Fig. 1 Some known drugs that contain a 1,2-disubstituted imidazole nucleus.

These new molecules can be obtained through viable, environmentally friendly synthetic routes. For this reason, in this research, we synthesize imidazoles anchored to simple amino acids such as phenylalanine, valine and alanine, demonstrating the viability of a 3-step synthetic route to introduce the amino acid at position 2 of the imidazole ring, as compared with a one-step method for substitution at position one. The synthetic route chosen is not complicated. It is based, first of all, on the synthesis of an imidazole ring starting from benzil—and an aldehyde such as *p*-nitrobenzaldehyde—in the presence of ammonium acetate and glacial acetic acid (as a solvent and catalyst simultaneously).

The nitrogen at position 1 of the imidazole ring originates from different sources depending on the reactant used (Fig. 2). When phenylalanine is introduced into the reaction medium, it occupies this position, affording an imidazole containing a phenylalanine fragment (54.9% yield), *via* one-step (one-pot) synthesis. In order to verify this route, an amino acid such as valine was also used (30.5% yield).

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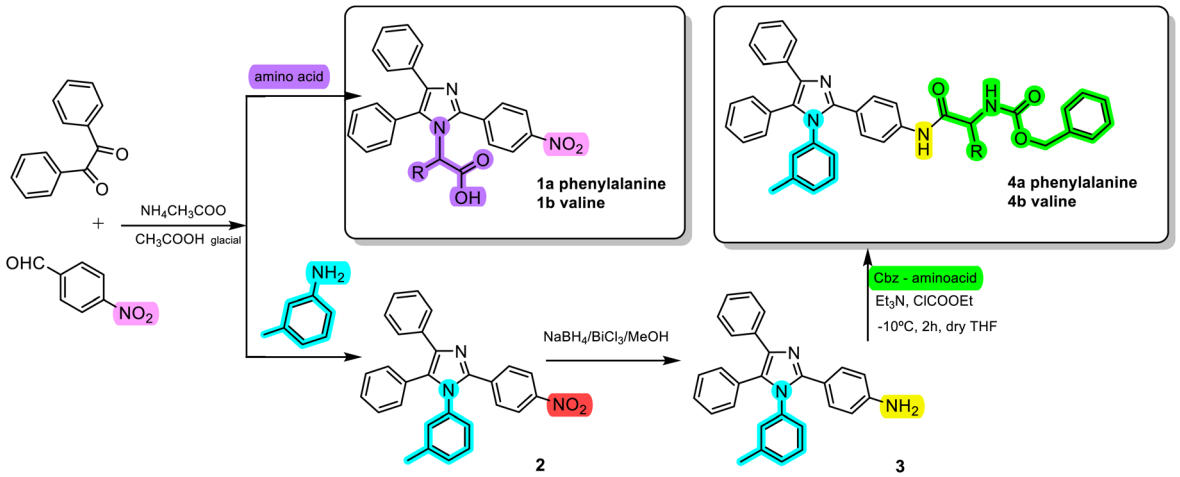

Fig. 2 Synthesis of tetrasubstituted imidazoles.

However, if an amino acid is replaced by an aromatic amine such as m-toluidine, it will be the one that occupies this position. This shows that the glacial acetic acid method apparently leads to good results in the formation of tetrasubstituted imidazoles, even when using less basic precursors such as amino acids and aromatic amines, compared to aliphatic amines and ammonium acetate itself.

The proposed reaction mechanism is based on the initial decomposition of ammonium acetate, thus generating a source of nitrogen, followed by the protonation of the carbonyl group of the aldehyde used, causing a nucleophilic addition with elimination of water (Fig. 3). This protonated imine then induces an electron-deficient sp^2 carbon that can react with the amino group of the amino acid, forming a diamine capable of interacting with benzil. Through two simultaneous condensations, the imidazole would be formed, losing two water molecules.[20]

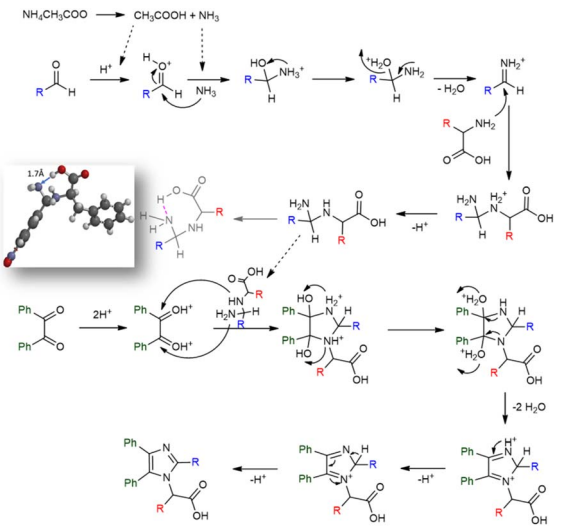

Fig. 3 Mechanism proposed for one-pot synthesis of amino acid tetrasubstituted imidazole.

So, how to bind an amino acid at position 2 of the imidazole? Observing that we have a nitro group, it is possible to take advantage of it as an anchor point, using the bismuth chemistry[21] to selectively reduce it to an amine group, giving, in this case, a conversion of 98%. This reduction guarantees the subsequent coupling of this imidazole with a Cbz-protected amino acid through the formation of an amide bond. The deprotection can be carried out, *a posteriori*, with H_2/Pd or HBr/CH_3COOH 33%. However, we decided to keep this compound in this mode to guarantee its storage, recommending its deprotection only before the next reaction.

The analysis of the FT-IR and ^{1}H NMR spectra for each compound indicates the viability of this route, showing the corresponding expected signals. Imidazole **1a**, obtained by a one-pot reaction, exhibits the expected signals in FT-IR and ^{1}H NMR (all this information can be found in SI). In the FT-IR spectrum, a broad band is shown at 3461 cm^{-1}, which can be assigned to the carboxyl group of the amino acid fragment added to the imidazole and which occupies position 1 of it. Similarly, a band at 1705 cm^{-1} is clearly observed, which is associated with the presence of this carboxyl group.[22]

Conversely, the ^{1}HNMR spectrum confirms the formation of compound **1a**, showing a singlet at exactly 13.88 ppm, likely corresponding to a proton exchangeable with water, based on the shape of the signal. This resonance is assigned to the hydrogen of the carboxyl group present in phenylalanine. Signals of hydrogens linked to aliphatic carbons are also identified, only existing in phenylalanine, as the rest of the molecule is aromatic.

The signals corresponding to aromatic protons appear between 6.74 and 8.33 ppm, integrating to a total of 19 protons, which matches the number of hydrogens present in all aromatic fragments of this imidazole. The presence of the nitro group can be evidenced through the doublet of 8.33 ppm (with integration of two protons) due to its shielding effect.[21] When analyzing the ^{1}HNMR spectrum of compound **1b**, all the expected signals for this imidazole are observed. However, other signals are noted in the spectrum attributable to the presence of

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appreciable amounts of trisubstituted imidazole, formed as a by-product in this reaction.[22]

For the tetrasubstituted imidazole **2**, the product of the inclusion of *m*-toluidine at position 1, the FT-IR spectrum clearly shows the vibrations ν_{Csp^3-H}, ν_{Csp^2-H}, ν_{NO_2}, in addition to those corresponding to the aromatic rings (see SI). When comparing this spectrum with that recorded for compound **3**, the disappearance of the vibration associated with the nitro group is noted, and instead, two bands appear at 3360 and 3206 cm^{-1}, which presumably correspond to the asymmetric and symmetric vibrations of the primary amino group resulting from the complete reduction of the nitro group of compound **2**.[20]

Conversely, the FT-IR spectrum of product **4a** indicates the successful coupling of an amino acid protected by a benzyloxycarbonyl (formerly carboxybenzyl or Cbz) group with imidazole **3**. In this case, a single band at 3316 cm^{-1} is observed, probably corresponding to stretching vibrations of the amide NH bond. The emergence of two carbonyl group bands (1820 and 1722 cm^{-1}) is also notable, suggesting the effective coupling of phenylalanine, which contains two carbonyls, including the Cbz group. In order to corroborate the above and characterize the products of this synthetic route, the ^{1}HNMR spectra of all the products were obtained.[22]

Distinctive expected signals were detected in each case (see SI). For example, compound **2** shows a chemical shift of 2.22 ppm, equivalent to 3 protons, in the form of a singlet, which shows the presence of the methyl group of the toluidine ring in the imidazole. If this spectrum is compared with that of compound **3**, it is possible to observe that this peak is maintained, but a new signal appears at 5.24 ppm, which is assigned to the amino group that is a product of the reduction performed with $NaBH_4/BiCl_3$.[21] Finally, the ^{1}HNMR spectrum of compound **4a** maintains the signal of the methyl group of the *m*-toluyl fragment, while other signals appear at 4.03 (doublet), 5.02 (triplet) and 5.75 ppm (singlet), which indicate the presence of the anchored protected amino acid (Fig. 4).[23] Furthermore, two singlet signals are noted at 9.7 and 7.0 ppm, which can be assigned to the hydrogen attached to the amide-type nitrogen atoms (one of them from the Cbz protecting group).[24]

The imidazoles substituted at position 2 obtained through this *in situ* activation–coupling method with ethyl chloroformate (see Fig. 2) show an interesting impurity pattern, which may correspond to traces of a by-product of the imidazole **3** with some excess of ethyl chloroformate, since a triplet and a quartet assignable to this molecule are observed.

In conclusion, it seems that the tetrasubstituted imidazole formation reaction works both for placing an amino acid at position 1 and an aromatic substituent. Similarly, the route developed for the inclusion of an amino acid at position 2 of the imidazole through three steps also appears to work. Both synthetic routes contain elements of sustainable chemistry, such as the use of benign solvents such as glacial acetic acid (which also acts as a catalyst), tetrahydrofuran and methanol. In addition, *in situ* activation of the amino acid phenylalanine during its coupling is applied using the ethyl chloroformate method.

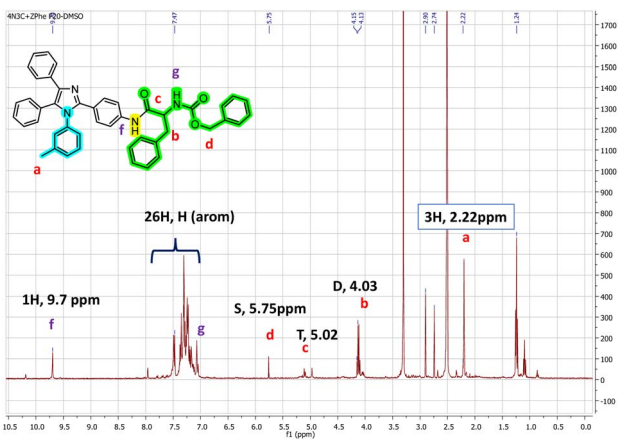

Fig. 4 ^{1}HNMR of imidazole **4a**: benzyl (1-((4-(4,5-diphenyl-1-(*m*-tolyl)-1*H*-imidazole-2-yl)phenyl)amino)-1-oxo-3-phenylpropan-2-yl) carbamate.

Author contributions

Conceptualization, A. F. and S. V. L.; methodology, A. F., Y. M., and L. E.; validation, S. C, S. V. L., and B. A.; formal analysis, Y. M., K. I. D., and L. E.; investigation, A. F., Y. M., L. E., and K. I. D.; writing original draft, A. F.; writing review and editing, A. F., S. C., and L. E.; visualization, A. F.; supervision, S. C., S. V. L. and B. A. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6ra01206j.

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