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Article

Heteroannulation Reaction of α-Aminoketones for the Efficient Synthesis of 4-Imidazolin-2-ones and 2-Thiones

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The hydrogenation of α-oximinoketones in methanol/HCl afforded α-aminoketones, which were applied without purification to the synthesis of 4-imidazolin-2-ones and 2-thiones, including chiral derivatives. The latter two series were obtained in high yields by a heteroannulation reaction of α-aminoketones with isocyanates and isothiocyanates, respectively. A double condensation of the α-aminoketones with two mol equivalents of the isocyanates produced a series of 4,5-dialkyl-*N*,3-diaryl-2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamides. With isothiocyanates, a single condensation reaction furnished a series of 4,5-dialkyl-1-aryl-1*H*-imidazole-2(3*H*)-thiones, which underwent alkylation with alkyl halides to form the corresponding 1-aryl-2-thioalkyl-1*H*-imidazoles in high yields.

Keywords: α-oximinoketones, α-aminoketones, 4-imidazolin-2-ones, 4-imidazolin-2-thiones, heteroannulation

Introduction

Substituted α-oximinoketones constitute versatile and attractive building blocks for the synthesis of numerous α-aminoketones[1,2] and azaheterocycles.[3-7] In particular, α-aminoketones exhibit strong pharmacological activity[8-10] and serve as common precursors of azaheterocyclic compounds.[6,11] 1*H*-Imidazole *N*-oxides are an example of azaheterocycles that can be readily constructed in one step by reacting α-oximinoketones with hexahydrotriazines,[12-14] revealing their broad synthetic potential.[15-18] Apart from providing antibacterial and antiparasitic activity,[19] 1*H*-imidazole *N*-oxides act as efficient substrates for the preparation of 4-imidazolin-2-ones.[20,21]

4-Imidazolin-2-ones, found in naturally occurring alkaloids,[22,23] are relevant heterocycles due to their pharmacological activity as antioxidants,[24] cytotoxic and antitumor agents,[25] D4 dopamine antagonists[26] and inhibitors of MurB enzyme.[27] Moreover, they can be included in the design of imidazole-containing new drugs.[28] Among the many methodologies developed for the synthesis of these versatile heterocycles[4,29-31] are the condensation of carbonyl compounds with substituted ureas[26,32] or isocyanates,[33] the

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intramolecular transposition of *N*-acyliminium species,[34] the transition metal-catalyzed insertion reactions,[35] the thermal reaction of α-aminoketones with isocyanates,[36] and the Ag(I)-catalyzed cycloisomerization of propargylic ureas.[37]

Analogous heterocycles are the 4-imidazolin-2-thiones and their 2-alkylthio-1*H*-imidazole derivatives. They have cytotoxic properties[25] and the capacity to inhibit various enzymes, such as 15-lipoxygenase (associated with diverse diseases, including atherosclerosis, cancer and inflammatory disorders),[38] cyclooxygenase, acyltransferase, and p38 MAP kinase.[11,39-41] Hence, there have also been intense efforts to design new and more efficient synthetic routes for the preparation of 4-imidazolin-2-thiones.[12,13] Among the possibilities thus far discovered are the reaction of benzoins, α-diketones, α-aminoketones or α-oximinoketones in the presence of ammonium thiocyanate,[42-44] isothioisocyanates[45] or thiourea.[46] The synthesis of their 2-alkylthio-1*H*-imidazole derivatives has been easily achieved by alkylation of the corresponding 4-imidazolin-2-thione precursor,[11,39,40] or by treatment of 1*H*-imidazole *N*-oxide derivatives with 2,2,4,4-tetramethylcyclobutane-1,3-dithiane.[12,47]

Our group recently reported the development of new 1*H*-imidazole *N*-oxide derivatives **3** via the reaction of functionalized α-oximinoketones **1** with chiral hexahydrotriazines **2**, and their conversion into imidazoline-based potential chiral auxiliaries **4** through a short and highly diastereoselective procedure.[21] As part of the ongoing effort to expand the scope of the synthetic applications of α-oximinoketones **1**, the aim of the current study was to transform these compounds into α-aminoketones **5**, to be used for the synthesis of a series of 4,5-disubstituted *N*,3-diaryl-2-oxo-2,3-dihydro-1*H*-imidazol-1-carboxamides **6** or 4,5-disubstituted 1-aryl-1*H*-imidazol-2(3*H*)-thiones **7** (Scheme 1).

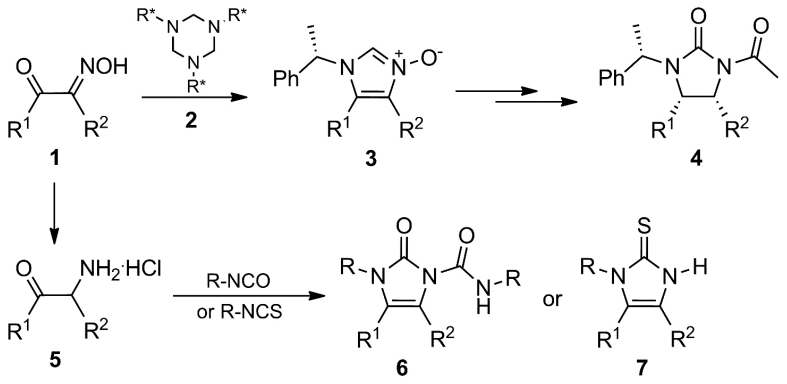
Results and Discussion

Synthesis of α-oximinoketones **1a**-**1d** was carried out by a previously described methodology (Scheme 2).[21] Briefly, α-oximinoketones **1a**-**1b** were prepared by treating the symmetrical α-diketones **8a**-**8b** with hydroxylamine hydrochloride. The reaction of the latter reagent with the unsymmetrical dione **8c** generated an inseparable mixture of two α-oximinoketones **1c**/**1d** (8:2). As a successful alternative, direct nitrosation conditions[1,48] of 2-pentanone (**8d**) and 3-pentanone (**8e**) afforded α-oximinoketones **1c** and **1d**, respectively, in good yield (Scheme 2).

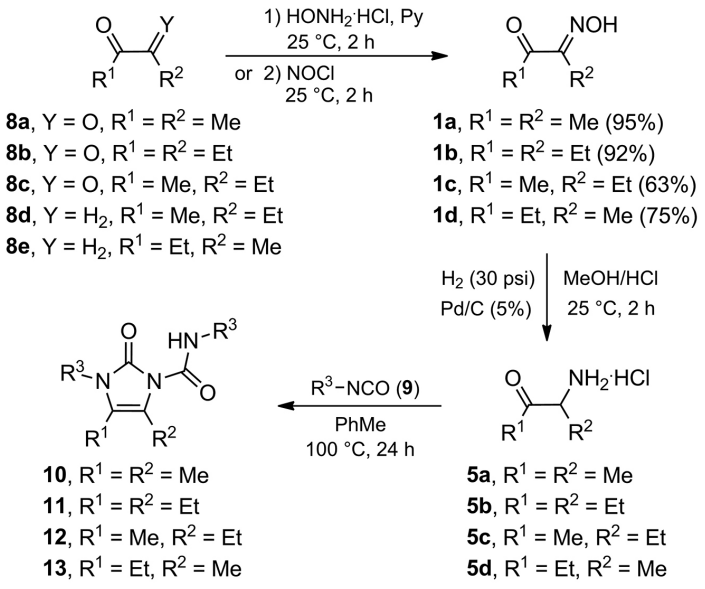
Through Pd(0)-catalyzed hydrogenolysis in the presence of hydrochloric acid,[33] α-oximinoketones **1a**-**1d** were converted into α-aminoketones **5a**-**5d**, their corresponding chlorhydrates (Scheme 2), in almost quantitative yields, as shown by the ^{1}H nuclear magnetic resonance (NMR) spectra of the crude mixtures. The isolation of the respective hydrochloride salts was necessary to avoid the dimerization of the free α-aminoketone.[49,50]

Without purification, α-aminoketones **5a**-**5d** were thermally reacted with isocyanates **9a**-**9i** to furnish the series of 2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamides **10**-**13** in moderate to good yields (Scheme 2, Table 1). Unexpectedly, the formation of imidazol-2-one **14** was not observed,[36] even when using a sub-equimolar amount of **9** (Scheme 3). Compound **14** was probably an intermediate in the formation of **10**-**13** via an N-addition of the unsubstituted nitrogen atom to another molecule of isocyanate. Considering that **14** was not detected in the crude reaction mixtures, the last step of the process is likely faster than the first step, which is the addition of the α-aminoketones **5a**-**5d** to arylisocyanates **9a**-**9i** to afford the carbamate intermediate **I** and the subsequent cyclization step to give hemiaminal **II**. However, it is also possible that the competitive intermolecular addition to **9** occurred from the internal urea moiety of **I** to generate intermediate **III**, followed by cyclization to provide **10**-**13**.[36]

There was no significant difference in efficiency between the products derived from alkyl or aryl



Scheme 1. Synthesis of imidazolidine- and imidazoline-based derivatives **4**, **6** and **7**.



Scheme 2. Synthesis of α-oximinoketones **1a**-**1d**, α-aminoketones **5a**-**5d** and 4-imidazolin-2-ones **10**-**13** (for R^3, see Table 1).

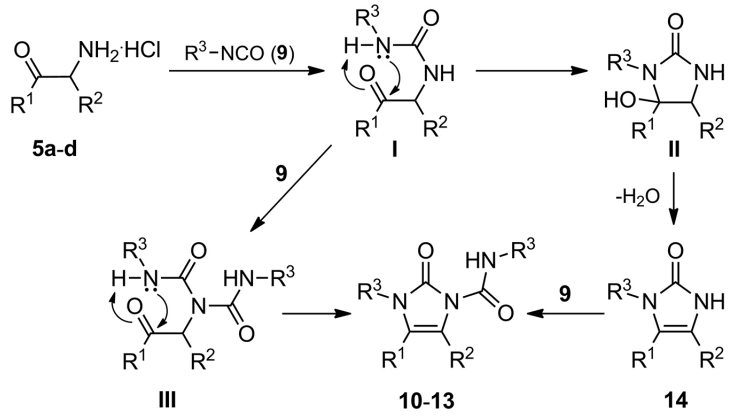
Table 1. Preparation of the series of 1*H*-imidazole-1-carboxamides **10**-**13** from the reaction of α-aminoketones **5a**-**5d** with isocyanates **9a**-**9i**[a]

entry	5	9	R^1	R^2	R^3	Product	Yield[b] / %
1	**5a**	**9b**	Me	Me	C_6H_4-3-Cl	**10a**	82
2	**5a**	**9d**	Me	Me	C_6H_4-4-Me	**10b**	80
3	**5a**	**9g**	Me	Me	C_2H_4-Cl	**10c**	87
4	**5b**	**9a**	Et	Et	C_6H_5	**11a**	85
5	**5b**	**9b**	Et	Et	C_6H_4-3-Cl	**11b**	90
6	**5b**	**9c**	Et	Et	C_6H_4-3-OMe	**11c**	88
7	**5b**	**9d**	Et	Et	C_6H_4-4-Me	**11d**	87
8	**5b**	**9f**	Et	Et	*n*-C_3H_7	**11e**	90
9	**5b**	**9h**	Et	Et	$CH_2CH{=}CH_2$	**11f**	88
10	**5b**	**9i**	Et	Et	(*S*)-CH(Me)Ph	**11g**	89
11	**5c**	**9a**	Me	Et	C_6H_5	**12a**	62
12	**5c**	**9d**	Me	Et	C_6H_4-4-Me	**12b**	69
13	**5c**	**9e**	Me	Et	C_6H_4-4-OMe	**12c**	72
14	**5c**	**9f**	Me	Et	*n*-C_3H_7	**12d**	57
15	**5c**	**9h**	Me	Et	$CH_2CH{=}CH_2$	**12e**	54
16	**5d**	**9i**	Et	Me	(*S*)-CH(Me)Ph	**13**	87

[a]Under N_2 atmosphere, with α-aminoketones **5a**-**5d** (1.0 mol equiv) and isocyanates **9a**-**9i** (2.5 mol equiv) in anhydrous toluene, at 100 °C for 24 h. [b]Yields were determined after column chromatography.

isocyanates. Interestingly, the optically active 1*H*-imidazol-1-carboxamides **11g** and **13** were also prepared in good yields. Actually, the relatively modest yields observed for the derivatives from α-aminoketone **5c** were probably due to a lower conversion during the hydrogenolysis of the α-oximinoketone **1c** or a higher decomposition of the product **5c**, judging by the byproducts observed in the reaction crude mixtures by thin layer chromatography (TLC) analysis.

The structure of novel 2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamides **10**-**13** was determined by NMR spectroscopy (supported by 2D experiments, heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond coherence (HMBC)), high-resolution mass spectrometry (HRMS), elemental analysis and X-ray crystallography. The single crystal structure of **12c** (Figure 1; for simplicity, only one of the two conformers contained in the asymmetric unit cell is shown, see "X-ray crystallographic structures of **12c** and **16a**" sub-section, Supplementary Information section) displays a relatively rigid conformation of the *N*-carboxamide moiety, which



Scheme 3. Plausible reaction mechanisms for the formation of 2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamides **10**-**13**.

is due to the formation of an N–H···O (1.941 Å) hydrogen bond between the exocyclic urea proton atom and the oxygen atom of the imidazol-2-one carbonyl group. Hence, the carboxamide carbonyl group is oriented toward the C-5 alkyl group and has a *quasi*-coplanar conformation (dihedral angle C5–N1–C1'–O2 = 2.6°) with respect to the plane of the heterocycle. This is probably the reason why the protons of the C-5 alkyl substituent undergo a deshielding effect and their signal is shifted downfield in comparison with the protons of the C-4 alkyl group. However, a shielding effect of the N-3 aryl ring on the latter alkyl group cannot be discarded.[51]

The plausible formation of 4-imidazolin-2-ones **14** and their attack on the isocyanates **9** to afford the respective 2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamides **10**-**13** is a large part due to the high reactivity of the isocyanates themselves.[52] This is in contrast to the lower reactivity of isothiocyanates, as was demonstrated in the reaction of α-hydroxyketones.[53] Therefore, the reactivity of α-aminoketones **5a**-**5b** with isothiocyanates **15a**-**15c** was evaluated under reaction conditions similar to those used for isocyanates **9** (Table 2). Indeed, 4-imidazolin-2-thiones **16**-**17** were obtained as the main products in good yields.

The structure of 4-imidazole-2-thiones **16**-**17** was examined by ^{1}H and ^{13}C NMR spectroscopy, HRMS and elemental analysis. Interestingly, in the ^{1}H NMR spectra of derivatives **16**, the C-5 methyl group is shifted upfield with regard to the C-4 methyl group, which is probably due to the shielding effect of the aryl ring located at the vicinal nitrogen atom. The X-ray crystallography of **16a** confirmed its structure (Figure 2), showing that the aryl ring adopts an almost orthogonal conformation in relation to the plane formed by the heterocyclic ring (dihedral angle C5–N1–C1'–C2' = –117.1°), similar to the descriptions of analogous heterocycles.[53-57] Unlike other five-membered heterocycles, in which the C-4 and C-5 substituents adopt a nonplanar conformation,[56] the C-4 and C-5 methyl groups are *quasi*-eclipsed from each other (dihedral angle C6–C4–C5–C7 = –0.8°), as was observed in the case of its analog, 4,5-dimethyl-4-oxazolin-2-thione **19**.[53]

Hence, 4-imidazolin-2-thiones **16**-**17** were obtained in the absence of the respective carboxamides **18**. The presence of the latter compound would have derived from

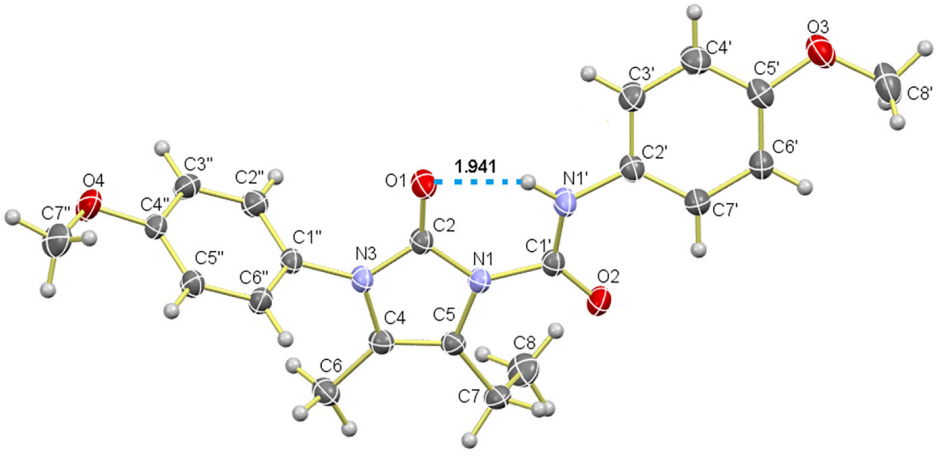
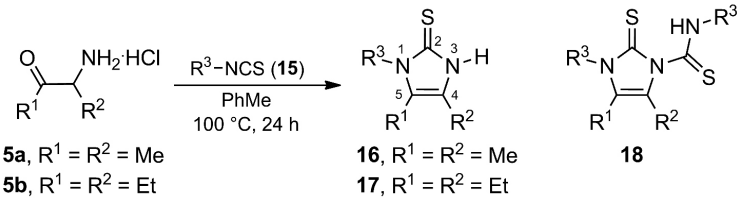


Figure 1. Structure of **12c** as determined by single-crystal X-ray diffraction (ellipsoids at the 30% probability level).

Table 2. Preparation of the series of 4-imidazolin-2-thiones **16**-**17** by the reaction of α-aminoketones **5a**-**5b** with isothiocyanates **15a**-**15c**[a]



5a, $R^1 = R^2 = Me$ **16**, $R^1 = R^2 = Me$ **18**
5b, $R^1 = R^2 = Et$ **17**, $R^1 = R^2 = Et$

entry	5	15	R^1	R^2	R^3	Product	Yield[b] / %
1	**5a**	**15a**	Me	Me	C_6H_4-3-Cl	**16a**	64
2	**5a**	**15b**	Me	Me	C_6H_4-3-Me	**16b**	67
3	**5a**	**15c**	Me	Me	C_6H_4-4-Cl	**16c**	68
4	**5b**	**15a**	Et	Et	C_6H_4-3-Cl	**17a**	73
5	**5b**	**15b**	Et	Et	C_6H_4-3-Me	**17b**	72
6	**5b**	**15c**	Et	Et	C_6H_4-4-Cl	**17c**	77

[a]Under N_2 atmosphere, with α-aminoketones **5a**-**5b** (1.0 mol equiv) and isothiocyanates **15a**-**15c** (2.5 mol equiv) in anhydrous toluene, at 100 °C for 24 h. [b]Yields were determined after column chromatography.

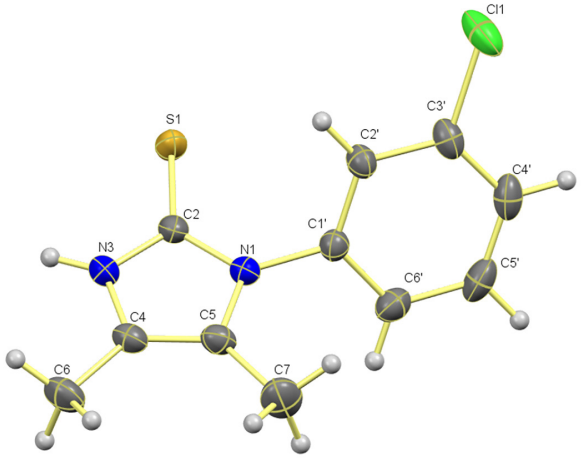


Figure 2. Structure of **16a** as determined by single-crystal X-ray diffraction (ellipsoids at the 30% probability level).

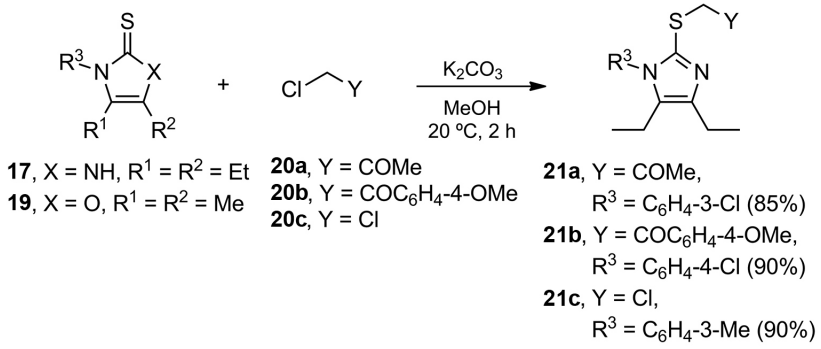
a subsequent attack of heterocycles **16-17** on a second molecule of the isothiocyanates **15a**-**15c**. The results may indicate that a second addition to **15a**-**15c** was impeded by the lower reactivity of the isothiocyanates, as well as the lower nucleophilicity of the N-3 nitrogen atom of 4-imidazole-2-thiones **16-17**. The observed behavior can be associated with the size of the sulfur atom and its 3d orbitals,[58] its high polarizability, as well as the hyperconjugation and inductive effect.[59,60] These factors induce the delocalization of the N-3 nitrogen lone-pair toward the C-2 carbon atom, and thus generate the aromatic character of the heterocycle of **16** and **17**. This occurs despite the lower electronegativity of the sulfur (2.58 D) *versus* nitrogen atom (3.05 D).

Our hypothesis is supported by the X-ray of compound **16a**. The distance of the N-3 and C-2 bond (1.343(2) Å) is shorter than that between N-1 and C-2 (1.361(3) Å), indicating a certain double bond character of the former. At the same time, a lengthening of the C2=S double bond should be expected. Indeed, the observed distance of C2=S was in fact longer (1.695(2) Å) than that for a known carbon disubstituted by nitrogen atoms $(Y)_2C{=}S$ (1.671 Å),[61] but shorter than a single $C(sp^2)$–S bond (1.751 Å).[61]

Consequently, the polarization of the electronic density of the N-3 nitrogen lone pair toward the C2=S bond should increase the electronic density at the sulfur atom, stabilizing a formal or incipient negative charge, then increasing its nucleophilicity.[59,60] The latter explains the attack of the sulfur atom on diverse electrophiles (**20a**-**20c**) to generate the imidazole-containing products **21a**-**21c** (Scheme 4). Of course, the N-3 nitrogen lone-pair polarization toward the heterocyclic ring reduces its nucleophilic effect, decreasing its reactivity with another molecule of the isothiocyanate and impeding the formation of compound **18**.

Another potential resemblance between 4-imidazolin-2-thiones **17** and 4-oxazolin-2-thiones **19** would be the ability of the sulfur atom to bind to electrophilic species, leading to the formation of aromatic 2-alkylthio-1*H*-imidazole derivatives.[39,40] If compound **19** undergoes addition to alkyl iodides to provide 2-(thioalkyl)oxazolium iodides,[53] compounds **17a**-**17c** will be able to react with electrophiles **20a**-**20c** under basic conditions to furnish the corresponding 2-(alkylthio)-1-aryl-4,5-diethyl-1*H*-imidazoles **21a**-**21c** in high yields (Scheme 4).

The greater capacity of the sulfur atom *versus* the nitrogen atom (or the enamine-like double bond) to react with electrophiles appears to stem from not only by its



Scheme 4. Synthesis of 2-(alkylthio)-1-aryl-4,5-diethyl-1*H*-imidazoles **21a**-**21c**.

nucleophilicity, but also by the polarization of the electron density of the nitrogen atom toward the thiocarbonyl group.[11,53] Of course, this effect is also favored by the stability resulting from the formation of a neutral aromatic heterocyclic ring.

Conclusions

The present methodology allows for access to 2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamides **10-13** through a heteroannulation reaction between α-aminoketones **5a**-**5d** and isocyanates **9a**-**9i** under thermal conditions, followed by an introduction of a second molecule of the isocyanate. On the other hand, the reaction of α-aminoketones **5a**-**5b** with isothiocyanates **15a**-**15c**, provided the series of 4-imidazole-2-thiones **16-17**, in which a second isothiocyanate was not incorporated. Heterocycles **17a-17c** underwent an S-alkylation leading to 2-(alkylthio)-1-aryl-4,5-diethyl-1*H*-imidazoles **21a**-**21c**.

Experimental

General

Melting points were determined on a Krüss KSP 1N capillary melting point apparatus. IR spectra were recorded on a PerkinElmer 2000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were captured on Varian Mercury (300 MHz) and Varian VNMR (500 MHz) instruments, with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as internal standard. Signal assignments were based on 2D NMR spectra (HMQC and HMBC). Mass spectra (MS) were recorded on Thermo Polaris Q-Trace GC Ultra and Hewlett-Packard 5971A spectrometers. High-resolution mass spectra (HRMS) were obtained (in electron impact mode) on a Jeol JSM-GCMateII spectrometer. Elemental analyses were performed on a CE-440 Exeter Analytical instrument. Analytical thin-layer chromatography was carried out by using E. Merck silica gel 60 F254 coated 0.25 plates, visualized with a long- and short-wavelength UV lamp. Flash column chromatography was conducted over Natland International Co. silica gel (230-400 and 230-400 mesh). All air moisture sensitive reactions were achieved under N_2 using oven-dried glassware. Prior to use, toluene was freshly distilled over sodium, as was CH_2Cl_2 over CaH_2. MeOH were distilled over sodium. K_2CO_3 was dried overnight at 200 °C prior to use. All other reagents (Sigma-Aldrich, St. Louis, MI, USA) were employed without further purification. Compounds **1a**-**1d** were prepared as described.[21]

Syntheses

3-Aminobutan-2-one hydrochloride (**5a**)

Under H_2 atmosphere (30 psi), a mixture of **1a** (0.500 g, 4.95 mmol) and Pd/C (5%) (0.05 g, 0.495 mol) in MeOH/HCl (37%) (9:1, 20 mL) was stirred at 25 ºC for 2 h. The reaction mixture was filtered and the solvent removed under vacuum to give **5a** as a reaction crude, which was used in the next step without previous purification.

4-Aminohexan-3-one hydrochloride (**5b**)

Following the method of preparation for **5a**, **1b** (0.500 g, 3.88 mmol) and Pd/C (5%) (0.039 g, 0.388 mol) were mixed under H_2 atmosphere to afford **5b** as a reaction crude, which was used in the next step without previous purification.

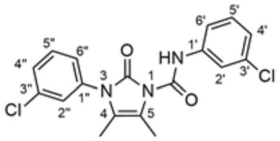
3-Aminopentan-2-one hydrochloride (**5c**)

Following the method of preparation for **5a**, **1c** (0.500 g, 4.35 mmol) and Pd/C (5%) (0.044 g, 0.435 mol) were mixed under H_2 atmosphere to furnish **5c** as a reaction crude, which was used in the next step without previous purification.

2-Aminopentan-3-one hydrochloride (**5d**)

Following the method of preparation for **5a**, **1d** (0.500 g, 4.35 mmol) and Pd/C (5%) (0.044 g, 0.435 mol) were mixed under H_2 atmosphere to provide **5d** as a reaction crude, which was used in the next step without previous purification.

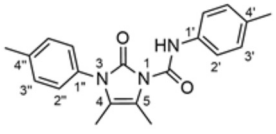
N,3-Bis(3-chlorophenyl)-4,5-dimethyl-2-oxo-2,3-dihydro-1*H* imidazole-1-carboxamide (**10a**)



10a

In a two-necked round-bottomed flask equipped with a thermometer and condenser, a mixture of **5a** (0.123 g, 1.00 mmol) and **9b** (0.382 g, 2.49 mmol) in anhydrous toluene (20 mL) was heated at 100 ºC for 24 h. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 98:2) to produce **10a** (0.31 g, 82%) as a white solid; Rf 0.53 (hexane/EtOAc, 8:2); mp 158-159 °C; IR (KBr) ν / cm^{-1} 3425, 3044, 2930, 1737, 1698, 1662, 1593, 1553, 1481, 1429, 1387, 1299, 1215, 1075, 781; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (br s, 3H, CH_3-4), 2.45 (br s, 3H, CH_3-5), 7.07 (ddd, *J* 7.8, 1.8, 1.2 Hz, 1H, H-6'), 7.19-7.25 (m, 2H, Ar-H), 7.27-7.35 (m, 2H, Ar-H), 7.43-7.47 (m, 2H, Ar-H), 7.75 (t, *J* 2.1 Hz, 1H, H-2'), 11.35 (s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 8.9 (*C*H_3-4), 11.9 (*C*H_3-5), 116.0 (C-4), 116.4 (C-5), 118.0 (C-6'), 120.1 (C-2'), 124.1 (C-4'), 125.8 (ArH), 127.9 (ArH), 129.0 (ArH), 129.9 (ArH), 130.5 (ArH), 134.67 (Ar), 134.69 (Ar), 135.1 (Ar), 138.6 (Ar), 148.2 (*C*ONH), 152.4 (C-2); MS (70 eV) *m/z*, 375 (M^+–1, 1), 153 (100), 125 (32), 90 (14), 63 (8); anal. calcd. for $C_{18}H_{15}Cl_2N_3O_2$: C, 57.46; H, 4.02; N, 11.17, found: C, 57.51; H, 4.05; N, 11.14.

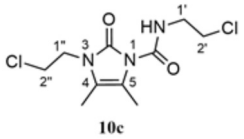
4,5-Dimethyl-2-oxo-*N*,3-di-*p*-tolyl-2,3-dihydro-1*H*-imidazole-1-carboxamide (**10b**)



10b

Following the method of preparation for **10a**, a mixture of **5a** (0.123 g, 1.00 mmol) and **9d** (0.33 g, 2.48 mmol) provided **10b** (0.268 g, 80%) as a white solid; Rf 0.56 (hexane/EtOAc, 8:2); mp 134-135 °C; IR (KBr) ν / cm^{-1} 3330, 3027, 2972, 1729, 1692, 1600, 1558, 1516, 1403, 1236, 1111, 820, 747; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (br s, 3H, CH_3-4), 2.30 (s, 3H, CH_3-4'), 2.40 (s, 3H, CH_3-4"), 2.44 (br s, 3H, CH_3-5), 7.11 (d, *J* 8.5 Hz, 2H, H-3'), 7.16 (d, *J* 8.5 Hz, 2H, H-2"), 7.29 (d, *J* 8.5 Hz, 2H, H-3"), 7.43 (d, *J* 8.5 Hz, 2H, H-2'), 11.30 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.8 (*C*H_3-4), 11.9 (*C*H_3-5), 20.7 (*C*H_3-4'), 21.1 (*C*H_3-4"), 115.3 (C-5), 116.6 (C-4), 120.1 (C-2'), 127.4 (C-2"), 129.4 (C-3'), 130.1 (C-3"), 131.1 (C-1"), 133.4 (C-4'), 134.9 (C-1'), 138.6 (C-4"), 149.2 (*C*ONH), 152.6 (C-2); MS (70 eV) *m/z*, 334 (M^+–1, 3), 133 (100), 104 (42), 91 (9), 78 (13), 51 (9); anal. calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53, found: C, 71.64; H, 6.35; N, 12.57.

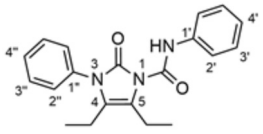
N,3-Bis(2-chloroethyl)-4,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamide (**10c**)



10c

Following the method of preparation for **10a**, a mixture of **5a** (0.100 g, 0.81 mmol) and **9g** (0.213 g, 2.00 mmol) furnished **10c** (0.197 g, 87%) as a white solid; Rf 0.19 (hexane/EtOAc, 8:2); mp 110-111 °C; IR (KBr) ν / cm^{-1} 3252, 2934, 1736, 1690, 1656, 1544, 1443, 1399, 1317, 1214, 751, 657; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04 (br s, 3H, CH_3-4), 2.31 (br s, 3H, CH_3-5), 3.65-3.70 (m, 4H, H-1', H-1"), 3.73 (t, *J* 5.0 Hz, 2H, H-2"), 3.91 (t, *J* 6.3 Hz, 2H, H-2'), 9.37 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.2 (*C*H_3-4), 11.7 (*C*H_3-5), 41.3 (C-2"), 41.6 (C-1'), 42.9 (C-2'), 43.2 (C-1"), 114.7 (C-5), 115.8 (C-4), 151.9 (*C*ONH), 152.8 (C-2); MS (70 eV) *m/z*, 279 (M^+–1, 4), 217 (5), 181 (8), 84 (100), 70 (13), 51 (73); anal. calcd. for $C_{10}H_{15}Cl_2N_3O_2$: C, 42.87; H, 5.40; N, 15.00, found: C, 42.83; H, 5.44; N, 14.96.

4,5-Diethyl-2-oxo-*N*,3-diphenyl-2,3-dihydro-1*H*-imidazole-1-carboxamide (**11a**)

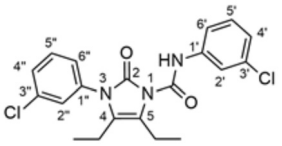


11a

Following the method of preparation for **10a**, a mixture of **5b** (0.15 g, 1.0 mmol) and **9a** (0.298 g, 2.50 mmol) gave **11a** (0.28 g, 85%) as a white solid; Rf 0.48 (hexane/EtOAc, 8:2); mp 129-131 °C; IR (KBr) ν / cm^{-1} 3449, 3035, 2972, 1729, 1690, 1596, 1560, 1493, 1401, 1234, 1111, 760, 692; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* 7.5 Hz, 3H, CH_3CH$_2$-4), 1.29 (t, *J* 7.2 Hz, 3H, CH_3CH$_2$-5), 2.36 (q, *J* 7.5 Hz, 2H, CH$_3$CH_2-4), 2.93 (q, *J* 7.2 Hz, 2H, CH$_3$CH_2-5), 7.09 (tm, *J* 7.8 Hz, 1H, H-4'), 7.28-7.36 (m, 4H, H-2", H-3"), 7.42-7.60 (m, 5H, H-2', H-3', H-4"), 11.42 (s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (*C*H$_3$CH$_2$-4), 15.3 (*C*H$_3$CH$_2$-5), 16.0 (CH$_3$*C*H$_2$-4), 18.7 (CH$_3$*C*H$_2$-5), 120.2 (C-2'), 121.1 (C-5), 122.4 (C-4), 123.9 (C-4'), 127.8 (C-2"), 128.8 (C-4"), 128.9 (C-3'), 129.6 (C-3"), 133.8 (C-1"), 137.5 (C-1'), 148.8 (*C*ONH), 152.9 (C-2); MS (70 eV) *m/z*, 335 (M^+, 2), 216 (59), 201 (100), 185 (12), 158 (16), 132 (15), 91 (43), 77 (9); HRMS (EI) *m/z*, calcd. for $C_{20}H_{21}N_3O_2$: 335.1634, found: 335.1637; anal. calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53, found: C, 71.65; H, 6.35; N, 12.54.

N,3-Bis(3-clorophenyl)-4,5-diethyl-2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamide (**11b**)

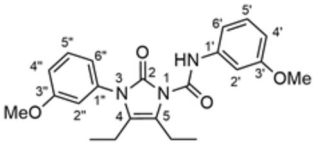
Following the method of preparation for **10a**, a mixture of **5b** (0.15 g, 1.0 mmol) and **9b** (0.384 g, 2.50 mmol) resulted in **11b** (0.361 g, 90%) as a white solid;



11b

Rf 0.53 (hexane/EtOAc, 8:2); mp 129-131 °C; IR (film) ν / cm^{-1} 3300, 3068, 2973, 2933, 1732, 1692, 1592, 1546, 1482, 1426, 1394, 1226, 777; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4), 1.28 (t, *J* 7.4 Hz, 3H, C*H*$_3$CH$_2$-5), 2.38 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 2.91 (q, *J* 7.4 Hz, 2H, CH$_3$C*H*$_2$-5), 7.01 (ddd, *J* 7.8, 1.5, 1.2 Hz, 1H, H-6'), 7.20-7.28 (m, 2H, ArH), 7.32 (ddd, *J* 8.4, 1.8, 1.2, 1H, ArH), 7.36 (t, *J* 2.0 Hz, 1H, H-2"), 7.43-7.51 (m, 2H, ArH), 7.76 (t, *J* 2.0 Hz, 1H, H-2'), 11.43 (s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (*C*H$_3$CH$_2$-4), 15.2 (*C*H$_3$CH$_2$-5), 16.0 (CH$_3$*C*H$_2$-4), 18.7 (CH$_3$*C*H$_2$-5), 118.1 (C-6"), 120.2 (C-2'), 121.6 (C-5), 122.2 (C-4), 124.1 (C-6'), 126.0 (ArH), 128.1 (ArH), 129.2 (ArH), 129.9 (ArH), 130.6 (ArH), 134.7 (Ar), 134.9 (Ar), 135.2 (Ar), 138.6 (Ar), 148.4 (*C*ONH), 152.7 (C-2); MS (70 eV) *m/z*, 403 (M$^+$, 10), 373 (16), 328 (16), 252 (11), 223 (10), 186 (16), 153 (100), 125 (21), 84 (51), 74 (25), 51 (33); HRMS (EI) *m/z*, calcd. for $C_{20}H_{19}N_3O_2Cl_2$ [M]$^+$: 403.0854; found: 403.0837; anal. calcd. for $C_{20}H_{19}N_3O_2Cl_2$: C, 59.42; H, 4.74; N, 10.39, found: C, 59.43; H, 4.78; N, 10.36.

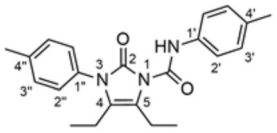
4,5-Diethyl-*N*,3-bis(3-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamide (**11c**)



11c

Following the method of preparation for **10a**, a mixture of **5b** (0.15 g, 1.0 mmol) and **9c** (0.373 g, 2.50 mmol) led to **11c** (0.344 g, 88%) as a white solid; Rf 0.43 (hexane/EtOAc, 8:2); mp 155-156 °C; IR (KBr) ν / cm^{-1} 3323, 3067, 2967, 1736, 1602, 1561, 1494, 1460, 1393, 1220, 1037, 778, 741, 689; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4), 1.28 (t, *J* 7.3 Hz, 3H, C*H*$_3$CH$_2$-5), 2.37 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 2.91 (q, *J* 7.3 Hz, 2H, CH$_3$C*H*$_2$-5), 3.78 (s, 3H, C*H*$_3$O), 3.83 (s, 3H, C*H*$_3$O), 6.65 (ddd, *J* 8.1, 2.4, 1.2 Hz, 1H, H-4'), 6.86 (t, *J* 2.4 Hz, 1H, H-2"), 6.91 (ddd, *J* 8.1, 2.1, 0.9 Hz, 1H, H-6"), 7.00 (ddd, *J* 8.1, 2.4, 0.9 Hz, 1H, H-4"), 7.13 (ddd, *J* 8.1, 2.1, 0.9 Hz, 1H, H-6'), 7.17-7.25 (m, 2H, H-2', H-5'), 7.41 (t, *J* 8.1 Hz, 1H, H-5"), 11.45 (s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (*C*H$_3$CH$_2$-4), 15.2 (*C*H$_3$CH$_2$-5), 15.9 (CH$_3$*C*H$_2$-4), 18.6 (CH$_3$*C*H$_2$-5), 55.2 (*C*H$_3$O), 55.4 (*C*H$_3$O), 105.5 (C-2'), 109.9 (C-4'), 112.3 (C-6'), 113.5 (C-2"), 114.5 (C-4"), 119.9 (C-6"), 121.1 (C-5), 122.3 (C-4), 129.6 (C-5"), 130.2 (C-5'), 134.8 (C-1"), 138.7 (C-1'), 148.5 (*C*ONH), 152.7 (C-2), 160.0 (C-3'), 160.3 (C-3''); MS (70 eV) *m/z*, 396 (M$^+$+1, 4), 246 (100), 233 (25), 231 (48), 182 (24), 149 (23); HRMS (EI) *m/z*, calcd. for $C_{22}H_{25}N_3O_4$ [M]$^+$: 395.1845, found: 395.1838; anal. calcd. for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63, found: C, 66.87; H, 6.41; N, 10.60.

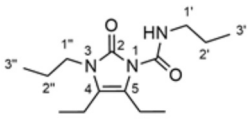
4,5-Diethyl-2-oxo-*N*,3-di-*p*-tolyl-2,3-dihydro-1*H*-imidazole-1-carboxamide (**11d**)



11d

Following the method of preparation for **10a**, a mixture of **5b** (0.15 g, 1.0 mmol) and **9d** (0.333 g, 2.50 mmol) gave **11d** (0.316 g, 87%) as a white solid; Rf 0.63 (hexane/EtOAc, 8:2); mp 131-132 °C; IR (KBr) ν / cm^{-1} 3330, 2972, 2932, 1729, 1692, 1600, 1559, 1516, 1403, 1237, 1112, 821, 748; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4), 1.27 (t, *J* 7.3 Hz, 3H, C*H*$_3$CH$_2$-5), 2.30 (s, 3H, C*H*$_3$-4'), 2.34 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 2.41 (s, 3H, C*H*$_3$-4"), 2.91 (q, *J* 7.3 Hz, 2H, CH$_3$C*H*$_2$-5), 7.10-7.35 (m, 2H, H-3'), 7.17-7.21 (m, 2H, H- 2"), 7.28-7.32 (m, 2H, H-3"), 7.41-7.45 (m, 2H, H-2'), 11.34 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (*C*H$_3$CH$_2$-4), 15.3 (*C*H$_3$CH$_2$-5), 16.0 (CH$_3$*C*H$_2$-4), 18.7 (CH$_3$*C*H$_2$-5), 20.8 (*C*H$_3$-4'), 21.2 (*C*H$_3$-4"), 120.2 (C-2'), 121.0 (C-5), 122.5 (C-4), 127.6 (C-2"), 129.5 (C-3'), 130.2 (C-3"), 131.3 (C-1"), 133.5 (C-4'), 135.0 (C-1'), 138.9 (C-4"), 148.9 (CONH), 153.0 (C-2); MS (70 eV) *m/z*, 362 (M$^+$–1, 10), 339 (9), 226 (10), 209 (12), 196 (13), 165 (69), 133 (90), 120 (100), 106 (65), 77 (85), 59 (50), 51 (89); HRMS (EI) *m/z*, calcd. for $C_{20}H_{25}N_3O_2$ [M]$^+$: 363.1947, found: 363.1950.

4,5-Diethyl-2-oxo-*N*,3-dipropyl-2,3-dihydro-1*H*-imidazol-1-carboxamide (**11e**)

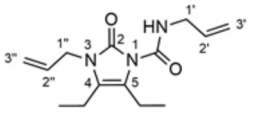


11e

Following the method of preparation for **10a**, a mixture of **5b** (0.15 g, 1.0 mmol) and **9f** (0.213 g, 2.50 mmol) afforded **11e** (0.241 g, 90%) as a yellow oil; Rf 0.50 (hexane/EtOAc, 8:2); IR (film) ν / cm^{-1} 3316, 2967, 2936, 1723, 1690, 1547, 1424, 1377, 1287, 1116, 763; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* 7.2 Hz, 3H, H-3"), 0.97 (t, *J* 7.2 Hz, 3H, H-3'), 1.12 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4), 1.16 (t, *J* 7.2 Hz, 3H, C*H*$_3$CH$_2$-5), 1.54-1.78 (m, 4H, H-2', H-2"), 2.40 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 2.78 (q, *J* 7.2 Hz, 2H, CH$_3$C*H*$_2$-5), 3.25-3.34 (m, 2H, H-1'), 3.49-3.57 (m, 2H, H-1"), 9.20 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.2 (C-3"), 11.5 (C-3'), 14.9 (*C*H$_3$CH$_2$-4), 15.3 (*C*H$_3$CH$_2$-5), 15.7 (CH$_3$*C*H$_2$-4), 18.5 (CH$_3$*C*H$_2$-5), 22.6 (C-2"), 22.8 (C-2'), 41.4 (C-1'), 42.6 (C-1"), 120.1 (C-5), 121.0 (C-4), 151.8

(*C*ONH), 153.0 (C-2); MS (70 eV) *m/z*, 266 (M^+–1, 1), 115 (62), 98 (89), 86 (90), 84 (100), 69 (14), 56 (55); HRMS (EI) *m/z*, calcd. for $C_{14}H_{25}N_3O_2$ $[M]^+$: 267.1947, found: 267.1946.

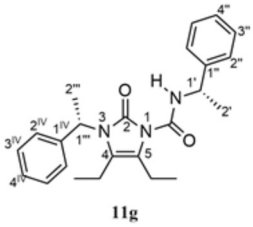
N,3-Diallyl-4,5-diethyl-2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamide (**11f**)



11f

Following the method of preparation for **10a**, a mixture of **5b** (0.15 g, 1.0 mmol) and **9h** (0.210 g, 2.50 mmol) produced **11f** (0.229 g, 88%) as a yellow oil, Rf 0.44 (hexane/EtOAc, 8:2); IR (film) ν / cm^{-1} 3428, 2975, 1722, 1687, 1645, 1542, 1432, 1401, 1258, 991, 923, 763; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4), 1.17 (t, *J* 7.2 Hz, 3H, C*H*$_3$CH$_2$-5), 2.39 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 2.80 (q, *J* 7.2 Hz, 2H, CH$_3$C*H*$_2$-5), 3.95-3.99 (m, 2H, H-1'), 4.23-4.26 (m, 2H, H-1"), 5.08 (d, *J* 17.5, 1H, H-3"), 5.14 (dd, *J* 10.0, 1.5 Hz, 1H, H-3'), 5.20 (dd, *J* 10.0, 1.0 Hz, 1H, H-3"), 5.26 (dd, *J* 17.5, 1.5 Hz, 1H, H-3'), 5.82-5.95 (m, 2H, H-2', H-2"), 9.27 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7 (*C*H$_3$CH$_2$-4), 15.2 (*C*H$_3$CH$_2$-5), 15.6 (CH$_3$*C*H$_2$-4), 18.4 (CH$_3$*C*H$_2$-5), 42.0 (C-1'), 43.0 (C-1"), 115.9 (C-3'), 116.6 (C-3"), 120.3 (C-5), 121.3 (C-4), 132.6 (C-2"), 134.0 (C-2'), 151.4 (*C*ONH), 152.9 (C-2); MS (70 eV) *m/z*, 261 (M^+–2, 4), 96 (100), 84 (20), 67 (7), 57 (43); HRMS (EI) *m/z*, calcd. for $C_{14}H_{21}N_3O_2$ $[M]^+$: 263.1634, found: 263.1629.

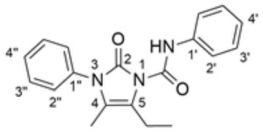
4,5-Diethyl-2-oxo-*N*,3-bis((*S*)-1-phenylethyl)-2,3-dihydro-1*H*-imidazole-1-carboxamide (**11g**)



11g

Following the method of preparation for **10a**, a mixture of **5b** (0.15 g, 1.0 mmol) and **9i** (0.367 g, 2.50 mmol) delivered **11g** (0.34 g, 89%) as a white solid; $[\alpha]^{27}_D$ –67.12 (*c* 0.132, MeOH); Rf 0.61 (hexane/EtOAc, 8:2); IR (film) ν / cm^{-1} 3201, 3030, 2973, 1720, 1682, 1536, 1450, 1382, 1258, 1217, 1067, 760, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4), 1.14 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-5), 1.53 (d, *J* 7.0 Hz, 3H, C*H*$_3$-2'), 1.86 (d, *J* 7.2 Hz, 3H, C*H*$_3$-2"'), 2.28 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 2.68-2.80 (m, 2H, CH$_3$C*H*$_2$-5), 5.08 (q, *J* 7.0 Hz, 1H, H-1'), 5.37 (q, *J* 7.2 Hz, 1H, H-1"'), 7.22-7.40 (m, 10H, Ar-H), 9.62 (d, *J* 7.5 Hz, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4 (*C*H$_3$CH$_2$-4), 15.2 (*C*H$_3$CH$_2$-5), 16.2 (*C*H$_3$CH$_2$-4), 18.2 (*C*H$_3$-2"'), 18.5 (CH$_3$*C*H$_2$-5), 22.9 (*C*H$_3$-2'), 49.7 (C-1'), 51.1 (C-1"'), 120.8 (C-5), 121.4 (C-4), 126.0 (C-2"), 126.4 (C-2^{IV}), 127.0 (C-4" or C-4^{IV}), 127.4 (C-4^{IV} or C-4"), 128.5 (C-3" or C-3^{IV}), 128.6 (C-3^{IV} or C-3"), 140.4 (C-1^{IV}), 143.8 (C-1"), 150.8 (*C*ONH), 152.9 (C-2); MS (70 eV) *m/z*, 147 (M^+–244, 47), 132 (100), 105 (30), 77 (20); HRMS (EI) *m/z* calcd. for $C_{24}H_{29}N_3O_2$ $[M]^+$: 391.2260, found: 391.2252; anal. calcd. for $C_{24}H_{29}N_3O_2$: C, 73.63; H, 7.47; N, 10.73, found: C, 73.61; H, 7.42; N, 10.77.

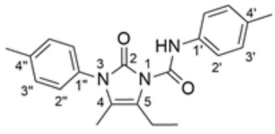
5-Ethyl-4-methyl-2-oxo-*N*,3-diphenyl-2,3-dihydro-1*H*-imidazole-1-carboxamide (**12a**)



12a

Following the method of preparation for **10a**, a mixture of **5c** (0.137 g, 1.00 mmol) and **9a** (0.298 g, 2.50 mmol) furnished **12a** (0.198 g, 62%) as a white solid; Rf 0.50 (hexane/EtOAc, 8:2); mp 144-145 °C; IR (KBr) ν / cm^{-1} 3449, 2975, 1738, 1693, 1598, 1562, 1497, 1393, 1215, 1107, 753; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, *J* 7.5 Hz, 3H, *C*H$_3$CH$_2$-5), 1.89 (s, 3H, *C*H$_3$-4), 2.92 (q, *J* 7.5 Hz, 2H, CH$_3$*C*H$_2$-5), 7.08 (t, *J* 7.5 Hz, 1H, H-4"), 7.29-7.32 (m, 4H, H-2", H-3"), 7.40-7.42 (m, 1H, H-4'), 7.49 (t, *J* 7.5 Hz, 2H, H-3'), 7.56 (d, *J* 7.5 Hz, 2H, H-2'), 11.39 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.7 (*C*H$_3$-4), 14.7 (*C*H$_3$CH$_2$), 18.8 (CH$_3$*C*H$_2$), 116.4 (C-4), 120.2 (C-2'), 121.4 (C-5), 123.9 (C-4'), 127.5 (C-2"), 128.6 (C-4"), 128.9 (C-3'), 129.4 (C-3"), 133.7 (C-1"), 137.5 (C-1'), 148.7 (*C*ONH), 152.7 (C-2); MS (70 eV) *m/z*, 320 (M^+–1, 5), 216 (44), 201 (100), 187 (20), 158 (17), 132 (23), 91 (36), 77 (50); anal. calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08, found: C, 71.08; H, 5.92; N, 13.12.

5-Ethyl-4-methyl-2-oxo-*N*,3-di-*p*-tolyl-2,3-dihydro-1*H*-imidazole-1-carboxamide (**12b**)

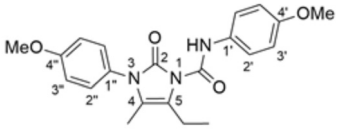


12b

Following the method of preparation for **10a**, a mixture of **5c** (0.137 g, 1.00 mmol) and **9d** (0.333 g, 2.50 mmol) provided **12b** (0.241 g, 69%) as a white solid; Rf 0.52 (hexane/EtOAc, 8:2); mp 140-141 °C; IR (KBr) ν / cm^{-1} 3424, 3031, 2929, 1731, 1600, 1559, 1515, 1400, 1320, 1290, 1240, 1107, 822, 749; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, *J* 7.3 Hz, 3H, C*H*$_3$CH$_2$-5), 1.87 (s, 3H, C*H*$_3$-4), 2.30 (s, 3H, C*H*$_3$-4'), 2.40 (s, 3H, C*H*$_3$-4"), 2.90 (q, *J* 7.2 Hz, 2H, CH$_3$C*H*$_2$-5), 7.11 (d, *J* 8.5 Hz, 2H, H-3'), 7.17 (d, *J* 8.5 Hz, 2H, H- 2"), 7.29 (d, *J* 8.5 Hz, 2H, H-3"), 7.44 (d, *J* 8.5 Hz, 2H, H-2'), 11.32 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.6 (*C*H$_3$-4), 14.7 (*C*H$_3$CH$_2$-5), 18.8 (CH$_3$*C*H$_2$-5), 20.7 (*C*H$_3$-4'), 21.1 (*C*H$_3$-4"), 116.4 (C-4), 120.2 (C-2'), 121.2 (C-5), 127.3 (C-2"), 129.4 (C-3'), 130.1 (C-3"), 131.1 (C-1"), 133.4

(C-4'), 135.0 (C-1'), 138.6 (C-4"), 148.8 (*C*ONH), 152.8 (C-2); MS (70 eV) *m/z*, 349 (M^+, 3), 133 (100), 104 (44), 84 (18), 51 (13); anal. calcd. for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03, found: C, 72.18; H, 6.64; N, 12.02.

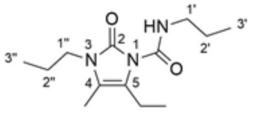
5-Ethyl-*N*,3-bis(4-methoxyphenyl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamide (**12c**)



12c

Following the method of preparation for **10a**, a mixture of **5c** (0.137 g, 1.00 mmol) and **9e** (0.373 g, 2.50 mmol) led to **12c** (0.274 g, 72%) as a pale yellow solid; Rf 0.24 (hexane/EtOAc, 8:2); mp 155-156 °C; IR (KBr) ν / cm^{-1} 3064, 2971, 1722, 1692, 1604, 1560, 1514, 1402, 1246, 1180, 1032, 824, 755; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, *J* 7.3 Hz, 3H, C*H*$_3$CH$_2$-5), 1.87 (s, 3H, C*H*$_3$-4), 2.90 (q, *J* 7.3 Hz, 2H, CH$_3$C*H*$_2$-5), 3.78 (s, 3H, C*H*$_3$O-4'), 3.85 (s, 3H, C*H*$_3$O-4"), 6.86 (d, *J* 9.0 Hz, 2H, H-3'), 7.00 (d, *J* 9.0 Hz, 2H, H-3"), 7.21 (d, *J* 9.0 Hz, 2H, H-2"), 7.46 (d, *J* 9.0 Hz, 2H, H-2'), 11.24 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.7 (*C*H$_3$-4), 14.8 (*C*H$_3$CH$_2$-5), 18.8 (CH$_3$*C*H$_2$-5), 55.4 (*C*H$_3$O-4'), 55.5 (*C*H$_3$O-4"), 114.1 (C-3'), 114.7 (C-3"), 116.6 (C-4), 121.0 (C-5), 121.9 (C-2'), 126.4 (C-1"), 128.8 (C-2"), 130.7 (C-1'), 149.0 (*C*ONH), 152.9 (C-2), 156.2 (C-4'), 159.6 (C-4"); MS (70 eV) *m/z*, 382 (M^++1, 1), 149 (100), 134 (60), 106 (39), 78 (14); anal. calcd. for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02, found: C, 66.16; H, 6.12; N, 11.00.

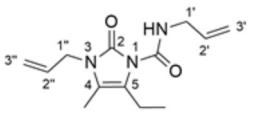
5-Ethyl-4-methyl-2-oxo-*N*,3-dipropyl-2,3-dihydro-1*H*-imidazole-1-carboxamide (**12d**)



12d

Following the method of preparation for **10a**, a mixture of **5c** (0.137 g, 1.00 mmol) and **9f** (0.213 g, 2.50 mmol) generated **12d** (0.144 g, 57%) as a pale orange oil; Rf 0.28 (hexane/EtOAc, 8:2); IR (film) ν / cm^{-1} 3265, 2966, 2934, 1724, 1687, 1655, 1550, 1460, 1398, 1257, 1214, 762; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J* 7.0 Hz, 3H, H-3"), 0.97 (t, *J* 7.0 Hz, 3H, H-3'), 1.14 (t, *J* 7.3 Hz, 3H, C*H*$_3$CH$_2$-5), 1.57-1.69 (m, 4H, H-2', H-2"), 2.00 (s, 3H, C*H*$_3$-4), 2.78 (q, *J* 7.3 Hz, 2H, CH$_3$C*H*$_2$-5), 3.27-3.32 (m, 2H, H-1'), 3.54 (t, *J* 7.0 Hz, 2H, H-1"), 9.17 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.9 (*C*H$_3$-4), 11.1 (C-3'), 11.2 (C-3"), 14.9 (*C*H$_3$CH$_2$-5), 18.4 (CH$_3$*C*H$_2$-5), 22.6 (C-2'), 22.7 (C-2"), 41.4 (C-1'), 42.5 (C-1"), 115.1 (C-4), 120.2 (C-5), 151.7 (*C*ONH), 152.9 (C-2); MS (70 eV) *m/z*, 253 (M^+, 6), 169 (15), 168 (100), 154 (11), 153 (89), 151 (13), 139 (6), 126 (14), 111 (38); anal. calcd. for $C_{13}H_{23}N_3O_2$: C, 61.63; H, 9.15; N, 16.59, found: C, 61.67; H, 9.11; N, 16.61.

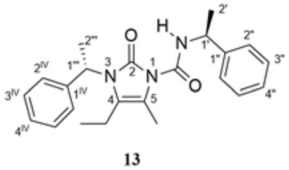
N,3-Diallyl-5-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxamide (**12e**)



12e

Following the method of preparation for **10a**, a mixture of **5c** (0.137 g, 1.00 mmol) and **9h** (0.208 g, 2.50 mmol) formed **12e** (0.134 g, 54%) as a pale yellow oil; Rf 0.26 (hexane/EtOAc, 8:2); IR (film) ν / cm^{-1} 3319, 2971, 2935, 1724, 1689, 1542, 1438, 1407, 1260, 1197, 922, 763; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-5), 1.98 (s, 3H, C*H*$_3$-4), 2.80 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-5), 3.94-3.99 (m, 2H, H-1'), 4.22-4.26 (m, 2H, H-1"), 5.08 (dd, *J* 17.5, 1.0 Hz, 1H, H-3"), 5.14 (dd, *J* 10.0, 1.5 Hz, 1H, H-3'), 5.19 (dd, *J* 10.0, 1.0 Hz, 1H, H-3"), 5.27 (dd, *J* 17.5, 1.5 Hz, 1H, H-3'), 5.80-5.96 (m, 2H, H-2', H-2"), 9.25 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8 (*C*H$_3$-4), 14.9 (*C*H$_3$CH$_2$-5), 18.4 (CH$_3$*C*H$_2$-5), 42.1 (C-1'), 43.0 (C-1"), 115.5 (C-4), 115.9 (C-3'), 116.7 (C-3"), 120.4 (C-5), 132.5 (C-2"), 134.0 (C-2'), 151.5 (*C*ONH), 152.8 (C-2); MS (70 eV) *m/z*, 250 (M^++1, 30), 249 (M^+, 9), 167 (18), 166 (100), 152 (20), 151 (54), 125 (19), 82 (9); HRMS (EI) *m/z*, calcd. for $C_{13}H_{19}N_3O_2$ $[M]^+$: 249.1477, found: 249.1464.

4-Ethyl-5-methyl-2-oxo-*N*,3-bis((*S*)-1-phenylethyl]-2,3-dihydro-1*H*-imidazole-1-carboxamide (**13**)



13

Following the method of preparation for **10a**, a mixture of **5d** (0.137 g, 1.00 mmol) and **9i** (0.373 g, 2.50 mmol) gave **13** (0.328 g, 87%) as a pale red oil; $[\alpha]^{29}_D$ –52.27 (*c* 0.066, MeOH); Rf 0.52 (hexane/EtOAc, 8:2); IR (film) ν / cm^{-1} 3246, 3030, 2974, 1720, 1685, 1536, 1451, 1377, 1291, 1217, 759, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4), 1.53 (d, *J* 7.2 Hz, 3H, C*H*$_3$-2'), 1.86 (d, *J* 7.2 Hz, 3H, C*H*$_3$-2"'), 2.25 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 2.27 (s, 3H, C*H*$_3$-5), 5.06 (q, *J* 6.9 Hz, 1H, H-1'), 5.40 (q, *J* 7.2 Hz, 1H, H-1"'), 7.20-7.42 (m, 10H, Ar-H), 9.59 (br d, *J* 7.5 Hz, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.6 (*C*H$_3$-5), 13.8 (*C*H$_3$CH$_2$-4), 16.2 (CH$_3$*C*H$_2$-4), 18.2 (*C*H$_3$-2"'), 22.9 (*C*H$_3$-2'), 49.7 (C-1'), 50.9 (C-1"'), 114.8 (C-5), 121.4 (C-4), 126.0 (C-2"), 126.3 (C-2^{IV}), 127.1 (C-4" or C-4^{IV}), 127.4 (C-4^{IV} or C-4"), 128.6 (C-3", C-3^{IV}), 140.3 (C-1^{IV}), 143.7 (C-1"), 151.3 (*C*ONH), 152.7 (C-2); MS (70 eV) *m/z*, 376 (M^+–H, 2), 147 (45), 132 (100), 105 (30), 77 (20); anal. calcd. for $C_{23}H_{27}N_3O_2$: C, 73.18; H, 7.21; N, 11.13, found: C, 73.18; H, 7.24; N, 11.18.

1-(3-Chlorophenyl)-4,5-dimethyl-1*H*-imidazole-2(3*H*)-thione (**16a**)

In a two-necked round-bottomed flask provided by a thermometer and condenser, a mixture of **5a** (0.123 g, 1.00 mmol) and **15a** (0.424 g, 2.50 mmol) in anhydrous toluene (20 mL) was heated at 100 ºC for 24 h. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 1:1) to give **16a** (0.14 g, 64%) as a yellow solid; Rf 0.56 (hex/AcOEt, 1:1); mp 110-112 °C; IR (film) ν / cm^{-1} 3086, 2921, 1592, 1494, 1384, 1352, 1243; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87 (s, 3H, CH_3-5), 2.11 (s, 3H, CH_3-4), 7.24-7.27 (m, 1H, H-6'), 7.33-7.35 (m, 1H, H-4'), 7.43-7.48 (m, 2H, H-2', H-5'), 11.62 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.1 (*C*H_3-5), 9.6 (*C*H_3-4), 120.7 (C-4), 122.1 (C-5), 126.8 (C-6'), 128.7 (C-4'), 129.3 (C-2'), 130.3 (C-5'), 134.9 (C-3'), 137.4 (C-1'), 160.2 (C-2); HRMS (EI) *m/z*, calcd. for $C_{11}H_{11}ClN_2S$ $[M]^+$: 238.0331, found: 238.0329.

4,5-Dimethyl-1-(*m*-tolyl)-1*H*-imidazole-2(3*H*)-thione (**16b**)

Following the method of preparation for **16a**, a mixture of **5a** (0.123 g, 1.00 mmol) and **15b** (0.373 g, 2.50 mmol) led to **16b** (0.146 g, 67%) as a yellow solid; Rf 0.50 (hexane/EtOAc, 1:1); mp 114-116 °C; IR (film) ν / cm^{-1} 3080, 2921, 1609, 1492, 1385, 1352, 1232, 768, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84 (s, 3H, CH_3-5), 2.11 (s, 3H, CH_3-4), 2.42 (s, 3H, CH_3-3'), 7.08-7.12 (m, 2H, H-2', H-6'), 7.26 (br d, *J* 8.0 Hz, 1H, H-4'), 7.40 (t, *J* 8.0 Hz 1H, H-5'), 11.44 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.1 (*C*H_3-4), 9.6 (*C*H_3-5), 21.3 (*C*H_3-3'), 120.2 (C-4), 122.4 (C-5), 125.3 (C-6'), 128.8 (C-2'), 129.2 (C-5'), 129.8 (C-4'), 136.3 (C-1'), 139.4 (C-3'), 159.9 (C-2); HRMS (EI) *m/z*, calcd. for $C_{12}H_{14}N_2S$ $[M]^+$: 218.0878, found: 218.0874.

1-(4-Chlorophenyl)-4,5-dimethyl-1*H*-imidazole-2(3*H*)-thione (**16c**)

Following the method of preparation for **16a**, a mixture of **5a** (0.123 g, 1.00 mmol) and **15c** (0.424 g, 2.50 mmol) gave **16c** (0.162 g, 68%) as a yellow solid; Rf 0.56 (hexane/EtOAc, 1:1); mp 111-112 °C; IR (film) ν / cm^{-1} 2922, 1496, 1400, 1350, 1269, 1255, 1089, 749; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (s, 3H, CH_3-5), 2.11 (s, 3H, CH_3-4), 7.26-7.29 (m, 2H, H-2'), 7.47-7.51 (m, 2H, H-3'), 11.89 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.0 (*C*H_3-4), 9.6 (*C*H_3-5), 120.8 (C-4), 122.1 (C-5), 129.7 (C-2'), 129.8 (C-3'), 134.8 (C-4'), 135.0 (C-1'), 159.9 (C-2); HRMS (EI) *m/z*, calcd. for $C_{11}H_{11}N_2SCl$ $[M]^+$: 238.0331, found: 238.0322.

1-(3-Chlorophenyl)-4,5-diethyl-1*H*-imidazole-2(3*H*)-thione (**17a**)

Following the method of preparation for **16a**, a mixture of **5b** (0.150 g, 1.00 mmol) and **15a** (0.424 g, 2.50 mmol) afforded **17a** (0.194 g, 73%) as a yellow solid; Rf 0.31 (hexane/EtOAc, 1:1); mp 203-204 °C; IR (KBr) ν / cm^{-1} 3069, 2930, 1651, 1593, 1495, 1394, 1231, 1072, 786, 771, 688; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* 7.5 Hz, 3H, CH_3CH$_2$-5), 1.21 (t, *J* 7.7 Hz, 3H, CH_3CH$_2$-4), 2.32 (q, *J* 7.5 Hz, 2H, CH$_3$CH_2-5), 2.50 (q, *J* 7.7 Hz, 2H, CH$_3$CH_2-4), 7.25-7.30 (m, 1H, H-6'), 7.33-7.37 (m, 1H, H-4'), 7.44-7.49 (m, 2H, H-2', H-5'), 12.3 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.1 (*C*H$_3$CH$_2$-5), 14.4 (*C*H$_3$CH$_2$-4), 16.9 (CH$_3$*C*H$_2$-5), 17.3 (CH$_3$*C*H$_2$-4), 126.8 (C-4), 127.0 (C-6'), 127.4 (C-5), 128.8 (C-4'), 129.4 (C-2'), 130.3 (C-5'), 134.8 (C-3'), 137.4 (C-1'), 159.7 (C-2); MS (70 eV) *m/z*, 266 (M^+, 100), 253 (47), 251 (74), 216 (68), 192 (43), 141 (69), 115 (39); HRMS (EI) *m/z*, calcd. for $C_{13}H_{15}ClN_2S$ $[M]^+$: 266.0644, found: 266.0642; anal. calcd. for $C_{13}H_{15}ClN_2S$: C, 58.53; H, 5.67; N, 10.50, found: C, 58.58; H, 5.62; N, 10.50.

4,5-Diethyl-1-(*m*-tolyl)-1*H*-imidazole-2(3*H*)-thione (**17b**)

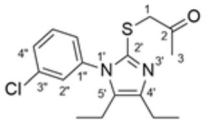
Following the method of preparation for **16a**, a mixture of **5b** (0.150 g, 1.00 mmol) and **15b** (0.373 g, 2.50 mmol) furnished **17b** (0.177 g, 72%) as a yellow solid; Rf 0.38 (hexane/EtOAc, 1:1); mp 182-183 °C; IR (KBr) ν / cm^{-1} 3152, 3066, 2969, 2928, 1650, 1609, 1590, 1494, 1457, 1395, 1231, 781, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* 7.5 Hz, 3H, CH_3CH$_2$-5), 1.20 (t, *J* 7.5 Hz, 3H, CH_3CH$_2$-4), 2.29 (q, *J* 7.5 Hz, 2H, CH$_3$CH_2-5), 2.42 (s, 3H, CH_3-3'), 2.49 (q, *J* 7.5 Hz, 2H, CH$_3$CH_2-4), 7.12 (br s, 1H, H-2'), 7.14 (br d, *J* 7.8 Hz, 1H, H-6'), 7.27 (br d, *J* 7.8 Hz, 1H, H-4'), 7.41 (t, *J* 7.8 Hz, 1H, H-5'), 12.30 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.2 (*C*H$_3$CH$_2$-5), 14.5 (*C*H$_3$CH$_2$-4), 16.9 (CH$_3$*C*H$_2$-5), 17.3 (CH$_3$*C*H$_2$-4), 21.3 (*C*H$_3$-3'), 125.5 (C-6'), 126.4 (C-4), 127.6 (C-5), 128.9 (C-2'), 129.1 (C-5'), 129.8 (C-4'), 136.3 (C-1'), 139.3 (C-3'), 159.2 (C-2); MS (70 eV) *m/z,* 246 (M^+, 100), 245 (50), 231 (51), 172 (44), 141 (26), 91 (18); HRMS (EI) *m/z*, calcd. for $C_{14}H_{18}N_2S$ $[M]^+$: 246.1191, found: 246.1194; anal. calcd. for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37, found: C, 68.29; H, 7.32; N, 11.32.

1-(4-Chlorophenyl)-4,5-diethyl-1*H*-imidazole-2(3*H*)-thione (**17c**)

Following the method of preparation for **16a**, a mixture of **5b** (0.150 g, 1.00 mmol) and **15c** (0.424 g, 2.50 mmol) provided **17c** (0.205 g, 77%) as a yellow solid; Rf 0.22 (hexane/EtOAc, 1:1); mp 204-205 °C; IR (KBr) ν / cm^{-1} 3157, 3077, 2970, 2934, 1651, 1496, 1399, 1378, 1231,

1090, 844, 804, 780, 740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-5), 1.21 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4), 2.31 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-5), 2.50 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 7.26-7.33 (m, 2H, H-2'), 7.44-7.47 (m, 2H, H-3'), 12.23 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.5 (*C*H$_3$CH$_2$-5), 14.7 (*C*H$_3$CH$_2$-4), 17.2 (CH$_3$*C*H$_2$-5), 17.6 (CH$_3$*C*H$_2$-4), 127.0 (C-4), 127.7 (C-5), 130.0 (C-2'), 130.2 (C-3'), 135.1 (C-1'), 135.3 (C-4'), 159.7 (C-2); MS (70 eV) *m/z*, 267 (M$^+$+1, 30), 266 (M$^+$, 100), 265 (26), 251 (58), 216 (32), 141 (45); HRMS (EI) *m/z*, calcd. for $C_{13}H_{15}N_2SCl$ [M]$^+$: 266.0644, found: 266.0645; anal. calcd. for $C_{13}H_{15}N_2SCl$: C, 58.53; H, 5.67; N, 10.50, found: C, 58.57; H, 5.71; N, 10.47.

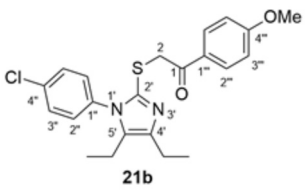
1-((1-(3-Chlorophenyl)-4,5-diethyl-1*H*-imidazol-2-yl)thio) propan-2-one (**21a**)


21a

In a round-bottomed flask (100 mL), a mixture of **17a** (0.322 g, 1.21 mol) and K_2CO_3 (0.167 g, 1.21 mmol) in dry MeOH (20 mL) was stirred at room temperature (rt) for 5 min. Then, **20a** (0.112 g, 1.21 mmol) was added and the mixture was stirred at rt for 2 h. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 8:2) to produce **21a** (0.33 g, 85%) as a yellow oil; Rf 0.50 (hexane/EtOAc, 8:2); IR (film) ν / cm^{-1} 3443, 2968, 1713, 1593, 1478, 1436, 789, 690; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-5'), 1.23 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4'), 2.25 (s, 1H, C*H*$_3$CO), 2.40 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-5'), 2.53 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4'), 3.82 (s, 2H, C*H*$_2$S), 7.19 (ddd, *J* 6.5, 2.1, 1.5 Hz, 1H, H-6"), 7.28-7.31 (m, 1H, H-4"), 7.41-7.49 (m, 2H, H-2", H-5"); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.5 (*C*H$_3$CH$_2$-5'), 14.6 (*C*H$_3$CH$_2$-4'), 16.9 (CH$_3$*C*H$_2$-5'), 20.4 (CH$_3$*C*H$_2$-4'), 28.6 (*C*H$_3$CO), 44.0 (*C*H$_2$S), 126.3 (C-6"), 128.1 (C-4"), 129.2 (C-2"), 130.3 (C-5"), 131.3 (C-5'), 134.8 (C-3"), 137.2 (C-1"), 137.8 (C-2'), 140.4 (C-4'), 203.0 (*C*OCH$_3$); MS (70 eV) *m/z*, 322 (M$^+$, 19), 307 (6), 295 (8), 281 (40), 279 (100), 277 (13), 265 (13), 247 (8), 230 (10), 111 (10); HRMS (EI) *m/z*, calcd. for $C_{16}H_{19}ClN_2OS$ [M]$^+$: 322.0907, found: 322.0901; anal. calcd. for $C_{16}H_{19}ClN_2OS$: C, 59.52; H, 5.93; N, 8.68; found: C, 59.56; H, 5.94; N, 8.64.

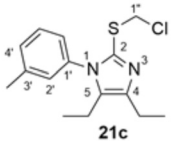
2-((1-(4-Chlorophenyl)-4,5-diethyl-1*H*-imidazol-2-yl)thio)-1-(4-methoxyphenyl)ethanone (**21b**)

Following the method of preparation for **21a**, a mixture of **17c** (0.226 g, 1.00 mmol), K_2CO_3 (0.138 g, 1.00 mmol) and **20b** (0.185 g, 1.00 mmol) generated **21b** (0.373 g, 90%) as a yellow oil; Rf 0.50 (hexane/EtOAc, 8:2); IR (film)


21b

ν / cm^{-1} 2968, 2931, 1608, 1590, 1491, 1447, 1377, 1233, 779, 726, 700, 658; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-5'), 1.26 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4'), 2.36 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-5'), 2.56 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4'), 3.87 (s, 3H, C*H*$_3$O), 4.38 (s, 2H, C*H*$_2$S), 6.87-6.91 (m, 2H, H-3"'), 7.02-7.07 (m, 2H, H-2"), 7.34-7.40 (m, 2H, H-3"), 7.82-7.90 (m, 2H, H-2"'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6 (*C*H$_3$CH$_2$-5'), 14.7 (*C*H$_3$CH$_2$-4'), 17.0 (CH$_3$*C*H$_2$-5'), 20.6 (CH$_3$*C*H$_2$-4'), 41.1 (*C*H$_2$S), 55.5 (*C*H$_3$O), 113.7 (C-3"'), 129.3 (C-2"), 129.4 (C-3"), 129.8 (C-1"'), 131.0 (C-2"'), 131.5 (C-5'), 134.7 (C-1"), 134.8 (C-4"), 138.1 (C-2'), 140.7 (C-4'), 163.8 (C-4"'), 192.8 (*C*OAr); MS (70 eV) *m/z*, 417 (M$^+$+3, 10), 416 (M$^+$+2, 16), 415 (M$^+$+1, 27), 414 (M$^+$, 26), 282 (13), 281 (45), 279 (100), 136 (14), 135 (19), 78 (6); HRMS (EI$^+$) *m/z*, calcd. for $C_{22}H_{23}N_2O_2SCl$ [M]$^+$: 414.1169, found: 414.1159.

2-((Chloromethyl)thio)-4,5-diethyl-1-(*m*-tolyl)-1*H*-imidazole (**21c**)


21c

Following the method of preparation for **21a**, a mixture of **17b** (0.246 g, 1.00 mmol), K_2CO_3 (0.138 g, 1.00 mmol) and **20c** (0.085 g, 1.00 mmol) formed **21c** (0.265 g, 90%) as a yellow oil; Rf 0.30 (hexane/EtOAc, 8:2); IR (film) ν / cm^{-1} 2924, 1671, 1599, 1494, 1260, 1171; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-5), 1.28 (t, *J* 7.5 Hz, 3H, C*H*$_3$CH$_2$-4), 2.42 (s, 3H, C*H*$_3$Ar), 2.43 (q, *J* 7.5 Hz, 1H, CH$_3$C*H*$_2$-5), 2.61 (q, *J* 7.5 Hz, 2H, CH$_3$C*H*$_2$-4), 4.94 (s, 2H, SC*H*$_2$Cl), 7.03-7.08 (m, 1H, H-6'), 7.06 (br s, 1H, H-2'), 7.29 (br d, *J* 7.5 Hz, 1H, H-4'), 7.37 (t, *J* 7.5 Hz, 1H, H-5'); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.5 (*C*H$_3$CH$_2$-5), 14.8 (*C*H$_3$CH$_2$-4), 17.1 (CH$_3$*C*H$_2$-5), 20.7 (CH$_3$*C*H$_2$-4), 21.3 (*C*H$_3$-3'), 50.2 (S*C*H$_2$Cl), 125.3 (C-6'), 128.8 (C-2'), 128.9 (C-5'), 129.8 (C-4'), 132.4 (C-5), 135.5 (C-3'), 135.9 (C-1'), 139.2 (C-2'), 141.1 (C-4); MS (70 eV) *m/z*, 297 (M$^+$+2, 37), 295 (M$^+$+1, 100), 294 (M$^+$, 41), 261 (15), 259 (26), 258 (20), 245 (12), 225 (8), 173 (6), 92 (7); HRMS (EI) *m/z*, calcd. for $C_{15}H_{19}N_2SCl$ [M]$^+$: 294.0957, found: 294.0943.

Single crystal X-ray crystallography

Compounds **12c** and **16a** were obtained as pale yellow crystals and crystallized on a mixture of hexane/EtOAc (8:2), which were mounted on glass fibers. Crystallographic measurements were performed by utilizing an area-

detector with Mo Kα radiation (λ = 71073 Å; graphite monochromator) at rt. Unit cell parameters were obtained from a least-squares refinement. Intensities were corrected for Lorentz and polarization effects. Absorption correction was applied by "multi-scan" method. Anisotropic temperature factors were introduced for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions and their atomic coordinates refined by employing unit weights. After the structure was solved using SHELXT,[62] it was visualized and plotted on the MERCURY program.[63] Data for **12c**: (CCDC 2045892) formula: $C_{21}H_{23}N_3O_4$; molecular weight: 381.42; cryst. syst.: triclinic; space group: P-1 (No. 2); unit cell parameters: *a* 9.7505(3), *b* 13.7423(3), *c* 15.9169(4) Å; α 72.242(2)º, β 87.170(2)º, γ 72.583(2)º; temp.: 292 K; Z: 4; No. of reflections collected: 26381; No. of independent reflections: 12126; No. of reflections observed: 8191; data collection range: $2.7 < \theta < 32.5$; *R*: 0.0579; GOF: 1.034. Data for **16a**: (CCDC 2045895) formula: $C_{11}H_{11}ClN_2S$; molecular weight: 238.73; cryst. syst.: triclinic; space group: P-1; unit cell parameters: *a* 6.6884(5), *b* 8.5311(8), *c* 11.7266(8) Å; α 105.893(7)°, β 94.236(6)°, γ 112.533(8)°; temp.: 293 K; Z: 2; No. of reflections collected: 12125; No. of independent reflections: 3880; No. of reflections observed: 2942; data collection range: $3.3 < \theta < 32.6$; *R*: 0.0549; GOF: 1.050.

Supplementary Information

Crystallographic data (excluding structure factors) for the structure in this work were deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 2045892 (for **12c**) and CCDC 2045895 (for **16a**). Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

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Author Contributions

A. R., R. B. and R. U. G. were responsible for experimental syntheses; C. E.-H. performed the X-ray diffraction analyses; A. M., and D. Z.-Z. recorded the MS and HRMS; E. I. M.-M. and E. M. L.-M. carried out the elemental analyses; M. A. V. and F. D. analyzed the experimental results and revised the manuscript; J. T. conceptualized the research, analyzed the results and wrote the manuscript.

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