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Imidazoles from nitroallylic acetates and $\alpha\text{-bromonitroalkenes}$ with amidines: synthesis and trypanocidal activity studies \dagger

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Cascade reactions of amidines with nitroallylic acetates and α -bromonitroalkenes provide potentially bioactive imidazoles in good to excellent yields in most cases. While 2,4-disubstituted imidazol-5-yl acetates are formed in the first case, 2,4-disubstituted imidazoles, bearing no substituent at position 5, are the products in the second case. These two series of imidazoles, *viz.* 2,4,5-trisubstituted and 2,4-disubstituted, were screened for their activity against the protozoan parasite *Trypanosoma cruzi* which is responsible for Chagas disease. As many as three compounds were as active as the standard benznidazole and two others were 2–3-fold more active highlighting the potential of substituted imidazoles, easily accessible from nitroalkenes, as possible anti-parasitic agents.

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Introduction

Several imidazole containing compounds exhibit activity against *Trypanosoma cruzi*, a parasite that causes Chagas disease. Synthesis and detailed evaluation of such anti-parasitic activity of imidazoles, including studies on their mechanism of action, have been reported in the recent literature. Other biological properties of imidazoles and their applications for the treatment of various diseases have also been well documented (Fig. 1). The presence of imidazoles in bio-

active compounds, including natural products,⁴ for instance, marine alkaloids,⁵ have received considerable attention. Potential applications of imidazoles in coordination chemistry⁶ and as precursors to ionic liquids⁷ and stable carbenes⁸ are also noteworthy.

Many new multi-component⁹ and metal-mediated^{10–12} approaches have appeared in the literature for the synthesis of imidazoles. However, the three component reaction of 1,2-dicarbonyl compound, aldehyde and ammonia, ¹³ and the reaction of (α -halo)ketones or diketones with formamide/amines ¹⁴ or amidines ¹⁵ are the classical ones. Reactions of amidines with acetylenes ¹¹ and nitroalkenes ¹² also lead to substituted imidazoles.

In essence, functionalized and fused imidazoles are attractive targets for synthetic chemists due to their diverse applications in chemistry and biology.¹⁶

From another perspective, the reactivity of conjugated nitroalkenes as substrates in reactions as diverse as Michael addition, Diels–Alder reaction, 1,3-dipolar cycloaddition and Morita–Baylis–Hillman reaction has been amply demonstrated. In particular, the Morita–Baylis–Hillman (MBH) reaction of nitroalkenes has emerged as a convenient means of synthesizing α -functionalized nitroalkenes which could in turn serve as excellent substrates for the synthesis of complex molecules. Several carbocycles and heterocycles have been synthesized exploiting the 1,2 or 1,3-bi-electrophilic character of the nitroallylic acetates through a cascade $S_{\rm N}2$ or $S_{\rm N}2'$ reaction of a binucleophile followed by an intramolecular Michael addition.

Among nitroalkenes, α -bromonitroalkenes, by virtue of their 1,2-bielectrophilic character, are capable of taking part in

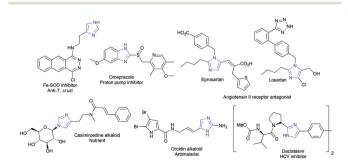


Fig. 1 Selected examples of bioactive imidazoles.

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cascade reactions with various binucleophiles. Their reaction with 1,3-dicarbonyl compounds, 23 enamines, 24 and other miscellaneous binucleophiles²⁵ provided various functionalized heterocycles such as furans, pyrroles, pyrazoles, and triazoles among others. However, to our knowledge, there is no report on the reaction of α -bromonitroalkenes with amidines for the synthesis of functionalized imidazoles.

This work describes the full version of our studies on the synthesis of imidazoles by treating amidines with nitroallylic acetates and α -bromonitroalkenes and studies on their trypanocidal activity.26

Results and discussion

In our recent communication,²⁶ we reported the synthesis of imidazole esters 3 from nitroallylic acetates 1 and amidines 2 through a one-pot cascade intermolecular aza-S_N2' reactionintramolecular aza-Michael addition (Table 1). Selected imidazole esters 3 were transformed to alcohols 4, acids 5 and then to amides 6 (Scheme 1). Many of these imidazoles were screened for their activity against the protozoan parasite T. cruzi, the etiological agent of Chagas disease. In particular, the activity of imidazole esters 3a and 3b was comparable to that of the standard benznidazole. More importantly, imidazole ester 3e exhibited activity twice that of benznidazole thus prompting us to synthesize and screen more imidazoles in this series and also those with other substitution patterns.

At the outset, imidazoles 3h, 3o and 3p (Table 1, entries 8, 15 and 16) and 4d, 5a, 5d, 6a and 6d (Scheme 1) which were reported in our previous communication, 26 but could not be screened earlier were later evaluated for their activity. Unfortu-

$$\begin{array}{c} \text{HN} \\ \text{Ar} \\$$

Scheme 1 Synthesis of derivatives of selected imidazole esters 3a and 3d and their activity against T. cruzi trypomastigotes. IC₅₀/24 h reported in µM. ^aNew compound. ^bIC₅₀/24 h was not reported in ref. 26.

Table 1 Synthesis of imidazoles 3 from nitroallylic acetates 1 and amidines 2 and their activity against T. cruzi trypomastigotes

Entry	1, R ¹	2, R ²	Time (h)	3	% Yield ^a	$IC_{50}/24 \text{ h } (\mu\text{M})^{b,c}$	
1	1a, 4 -MeOC ₆ H ₄	C_6H_5		3a		111.9 ± 15.4	
2	1b , 2,4-(MeO) $_2$ C ₆ H ₃	C_6H_5	4	3 b	68	102.0 ± 10.3	
3	1c, $3,4-(MeO)_2C_6H_3$	C_6H_5	3	3 c	86	236.2 ± 16.4	
4	1d , 5-Benzo[d][1,3]dioxole	C_6H_5	2	3 d	91	193.0 ± 08.6	
5	1e, 4 -MeC ₆ H ₄	C_6H_5	3	3 e	91	51.1 ± 04.3	
6	$1f, C_6H_5$	C_6H_5	4	3f	89	561.7 ± 56.6	
7	$1g, 4-FC_6H_4$	C_6H_5	2	3g	68	256.6 ± 21.9	
8	$\mathbf{1h}$, 4 -ClC ₆ H ₄	C_6H_5	0.5	3h	67	213.9 ± 22.8^d	
9	1i , 3-BrC ₆ H ₄	C_6H_5	0.5	3i	65	187.5 ± 05.5	
10	1j, 1-Naphthyl	C_6H_5	4	3j	67	190.8 ± 02.3	
11	1k, 2-Furyl	C_6H_5	7	3k	74	1002.6 ± 76.8	
12	1l, 2-Thienyl	C_6H_5	2	31	62	734.9 ± 41.8	
13	$1m$, C_6H_5CH = CH	C_6H_5	1.5	3m	58	382.2 ± 46.7	
14	1n, Cyclohexyl	C_6H_5	1	3n	67	172.0 ± 00.8	
15	$10, C_6H_5$	$4\text{-MeC}_6\text{H}_4$	2	30	69	192.7 ± 21.6^d	
16	1p , C_6H_5	$4-ClC_6H_4$	1.5	3 p	54	194.5 ± 14.4^d	
17	$1q, C_6H_5$	$3-ClC_6H_4$	1	3q	88	221.2 ± 28.2	
18	$1r, C_6H_5$	CH_3	1	3r	62	946.7 ± 12.2	
19	1s, C_6H_5	CH_3S	1.5	3s	32	1402.3 ± 260	
20	1t, $3,4-(MeO)_2C_6H_3$	$4\text{-ClC}_6\text{H}_4$	2.5	3t	63	>600 ^e	
21	1u, 3.4 -(MeO) ₂ C ₆ H ₃	3-ClC ₆ H ₄	1	3u	67	>600 ^e	
22	$1v, 3, 4-(MeO)_2C_6H_3$	4-MeC ₆ H ₄	2.5	3v	63	>1000 ^e	

^a After purification by column chromatography. ^b Mean ± SD of at least 3 independent experiments. ^c Positive control: benznidazole IC₅₀ 103.6 ± 0.6. ^d IC₅₀/24 h was not reported in ref. 26. ^e New compound.

nately, none of them yielded positive results. While 3h, 3o and 3p showed activity approximately half (IC₅₀/24 h in the range of 190-214 µM) of that of the standard, benznidazole (IC₅₀/ 24 h 103.6 μM), the other derivatives 4d, 5a, 5d, 6a and 6d did not show any activity at all (IC₅₀/24 h > 300 μ M).

In view of the above, imidazole esters 3t-v were synthesized following the general procedure reported by us earlier (Table 1, entries 20-22). Additionally, imidazole ester 3a was transformed to alcohol 4a using LAH in 76% yield and alcohol 4a, in turn, was converted to azide 7a in 60% yield (Scheme 1). Subsequently, esters 3t-v, alcohol 4a and azide 5a were subjected to trypanocidal activity studies as reported before. However, while esters 3t-v and alcohol 4a were inactive, azide 7a showed only moderate activity (IC₅₀/24 h 157.3 μ M). It is worth mentioning the potential of the clickable imidazole 7a that can be considered as an important intermediate in click chemistry reactions for the synthesis of hybrid compounds.

In the above scenario, we decided to explore the possibility of synthesizing imidazoles with different substitution patterns by our own methodology and screen them for their trypanocidal activity. Interestingly, although synthesis of imidazoles of type 9 via various miscellaneous methods is known in the literature, $^{27-36}$ the reaction of amidines 2 with α -bromonitroalkenes 8 has not been employed for such purposes. At the outset, amidine 2a and α-bromonitroalkene 8a were chosen as model substrates in order to establish the optimal conditions (Table 2).

There was no appreciable conversion when 1 equiv. of Cs₂CO₃ was employed as a base in THF at room temperature even after 24 h (entry 1). However, upon increasing the loading of Cs₂CO₃ to 2 and 3 equiv., there was a dramatic rise in the product yields to 55% and 85% as well as an improvement in the reaction rate to 18 h and 12 h, respectively (entries 2 and 3). While K₂CO₃ also gave comparable yields (80%) of the product 9a (entry 4), amine bases such as DMAP, DABCO and Et₃N were less effective (entries 5-7) under otherwise identical

Table 2 Optimization studies for the synthesis of imidazole 9a from α -bromonitroalkene 8a and amidine 2a

Ar
$$\frac{NO_2}{Br}$$
 $+\frac{NH_2}{Ph}$ $\frac{Cl}{NH_2}$ $\frac{base}{solvent, RT}$ $\frac{HN}{N}$ $\frac{Ar}{Ar}$ $\frac{8a}{2a}$ $\frac{Ar}{Ar}$ $\frac{4r}{Ar}$ $\frac{4r}{Ar$

Entry	Base (equiv.)	Solvent	Time (h)	% Yield
1	Cs ₂ CO ₃ (1)	THF	24	b
2	$Cs_2CO_3(2)$	THF	18	55
3	$Cs_2CO_3(3)$	THF	12	85
4	$K_2CO_3(3)$	THF	12	80
5	DMAP (3)	THF	12	56
6	DABCO (3)	THF	12	61
7	NEt ₃ (3)	THF	12	49
8	Cs_2CO_3 (3)	CH_3CN	3	93
9	$Cs_2CO_3(3)$	Toluene	5	75

^a After silica gel column chromatography. ^b No reaction.

conditions. Finally, changing solvent to CH3CN enabled us to improve the yield further to 93% and considerably reduce the reaction time to 3 h (entry 8) though the yield was much lower (75%) in a hydrocarbon solvent such as toluene (entry 9).

The above optimized conditions were successfully employed for the synthesis of a variety of 2,5-disubstituted imidazoles 9 and 10 (Tables 3 and 4). Initially, benzamidine 2a was treated with bromonitroalkenes 8 bearing various substituents at the β-position to afford imidazoles 9 (Table 3). In particular,

Table 3 Synthesis of imidazoles 9 from α -bromonitroalkenes 8 and amidine 2a

Entry	8	R	Time (h)	9	% Yield ^a	$IC_{50}/24 \text{ h} \ (\mu\text{M})^{b,c}$
1	8a	4-MeOC ₆ H ₄	3.0	9a	93	177.2 ± 20.7
2	8b	$3,4-(MeO)_2C_6H_3$	3.0	9b	92	372.5 ± 29.9
3	8c	5-Benzo[d][1,3]dioxole	3.0	9c	90	194.5 ± 14.2
4	8d	C ₆ H ₅	3.0	9d	88	377.2 ± 37.6
5	8e	4-MeC ₆ H ₄	3.0	9e	92	240.6 ± 32.9
6	8f	4-MeSC ₆ H ₄	6.0	9f	84	256.2 ± 9.8
7	8g	4-ClC ₆ H ₄	4.5	9g	86	332.2 ± 41.9
8	8h	$4\text{-FC}_6\text{H}_4$	4.5	9ĥ	76	329.8 ± 33.1
9	8i	$3-BrC_6H_4$	4.0	9i	74	339.4 ± 16.5
10	8j	$2-O_2NC_6H_4$	5.0	9j	85	395.2 ± 5.3
11	8k	2-Thienyl	4.5	9k	85	352.1 ± 16.5
12	81	3-Thienyl	5.0	91	71	355.3 ± 3.0
13	8m	1-Naphthyl	5.5	9m	81	35.5 ± 4.3
14	8n	$C_6H_5CH = CH$	6.0	9n	67	157.8 ± 23.6
15	80	Cyclohexyl	5.0	90	85	99.6 ± 5.2
16	8p	<i>n</i> -Butyl	5.0	9p	75	151.1 ± 3.2

^a After silica gel column chromatography. ^b Mean ± SD of at least 3 independent experiments. c Positive control: benznidazole IC₅₀ 103.6 \pm 0.6.

Table 4 Synthesis of imidazoles 10 from α -bromonitroalkene 8a and amidines 2

Entry	2	R	Time (h)	10	% Yield ^a	$IC_{50}/24 \text{ h } (\mu\text{M})^{b,c}$
1	2b	4-MeC ₆ H ₄	3.5	10b	87	123.0 ± 13.9
2	2c	$4-ClC_6H_4$	4.0	10c	79	182.6 ± 16.5
3	2d	$3-ClC_6H_4$	3.5	10d	83	184.4 ± 7.1
4	2e	MeS	5.0	10e	55	213.8 ± 14.6
5	2f	NH_2	2.0	10f	d	_
6	2g	Н	3.0	10g	d	_

^a After silica gel column chromatography. ^b Mean ± SD of at least 3 independent experiments. ^c Positive control: benznidazole IC_{50} 103.6 \pm 0.6. ^d Complex mixture.

bromonitroalkenes bearing electron rich aryl groups at the β-position 8a-c and 8e provided the products 9a-c and 9e, respectively, in excellent yield (>90%, entries 1-3 and 5). The only exception among nitroalkenes bearing an electron rich aryl group was 8f which afforded the product 9f in a slightly lower yield (84%) and a longer reaction time (6 h, entry 6). The yields of imidazoles derived from nitroalkenes bearing parent phenyl 8d, electron deficient aryls 8g-j and a fused aryl 8m at the β -position were in the range of 74–88% (entries 4, 7–10 and 13). Heteroaryl substituted bromonitroalkenes 8k-l also delivered the corresponding imidazoles 9k-l in good to high vield (71-85%, entries 11 and 12). While bromonitrodiene 8n afforded the product 9n in moderate yield (67%, entry 14), β-alkylated nitroalkenes 80 and p were better substrates and provided the desired imidazoles 90-p in 75-85% yield (entries 15 and 16).

Having demonstrated the wide scope of bromonitroalkenes 8 in the reaction with amidine 2a, the scope of amidines 2 was investigated by taking bromonitroalkene 8a as the representative substrate (Table 4). The reaction of 8a proceeded well with various arylamidines 2b-d to afford the products 10b-d in high yield (79-87%, entries 1-3). However, lower yield of imidazole 10e was encountered with thioamidine 2e (55%, entry 4). Guanidine 2f and formamidine 2g were not suitable substrates for the synthesis of imidazoles 10f-g as complex mixtures were isolated under our experimental conditions (entries

The structure and regiochemistry of imidazoles 9 and 10 were confirmed by comparison of their spectral data with those reported in the literature. In the proposed mechanism, the free amidine I derived from the neutralization of amidinium hydrochloride 2 by a base adds to bromonitroalkene 8 in a Michael fashion to afford intermediate II. Intramolecular nucleophilic substitution of bromide in II in a 5-exo-tet fashion provides the cyclized intermediate nitroimidazoline III which then undergoes base mediated elimination of HNO2 to give the product 2,5-disubstituted imidazole 9 or 10 (Scheme 2).

Scheme 2 Possible mechanism for formation of imidazoles 9 and 10 via [3 + 2] cycloaddition of amidines 2 with bromonitroalkenes 8.

Trypanocidal activity studies

In the case of imidazoles 3-7 derived from nitroallylic acetates 1, the most active compound was imidazole ester 3e (2-fold more potent than the current drug benznidazole) followed by esters 3b and then 3a, presenting IC₅₀/24 h values of 51.1, 102.0 and 111.9 μM, respectively. These three imidazoles possess a phenyl group at position 2 and an aryl group at position 5 bearing weakly or strongly electron donating substituent(s) at the ortho/para position(s). The presence of groups such as CH₂CO₂H, CH₂CONH₂, CH₂CH₂OH, and CH₂CH₂N₃ at position 5 did not improve the activity as compared to CH₂CO₂Et (Scheme 1 and Table 1). This was also a motivating factor to synthesize imidazoles of types 9 and 10 wherein there is no substituent at position 5. The evaluation of the IC50 values of imidazoles 9 and 10 in Tables 3 and 4 reveal that imidazole 9m bearing a phenyl group at position 2 and a naphthyl group at position 4 is 3-fold more active ($IC_{50}/24$ h = 35.5 μ M, Table 3, entry 13) than the standard benznidazole. This is followed by 90 with a phenyl group at position 2 and a cyclohexyl group at position 4 (IC₅₀/24 h = 99.6 μ M, Table 3, entry 15) which is as active as benznidazole. Imidazole 10b with a p-tolyl group at position 2 and a p-anisyl group at position 4 (IC₅₀/ 24 h = 123.0 μM, Table 4, entry 1) is marginally less active than benznidazole. Other analogs that show appreciable activity which is attributable to the substituents at positions 2 and 4 are **9p** (Ph, *n*-Bu, IC₅₀/24 h = 151.1 μ M, Table 3, entry 16), **9n** (Ph, styrenyl, $IC_{50}/24 \text{ h} = 157.8 \mu\text{M}$, Table 3, entry 14), 9a (Ph, *p*-anisyl, $IC_{50}/24 \text{ h} = 177.2 \mu\text{M}$, Table 3, entry 1), **10c** (*p*-anisyl, $p\text{-ClC}_6H_4$, $IC_{50}/24$ h = 182.6 μ M, Table 4, entry 2), 10d (p-anisyl, m-ClC₆H₄, IC₅₀/24 h = 184.4 μ M, Table 4, entry 3) and 9c (Ph, benzo[d][1,3]dioxole, $IC_{50}/24$ h 194.5 μ M, Table 3, entry 3).

In general, our compounds possess low molecular weight, partition coefficient and polar surface area values adhering to the Lipinski's rules. For the compounds described herein, the hydrophobicity appears sufficient for penetrating the biological membranes of the parasite, as determined by Lipinski's rule of 5 (clog P < 5, molecular weight ≤ 500 , and PSA $\leq 140 \text{ Å}^2$, number of hydrogen bond acceptors <10 and donors <5).37 Finally, a chemical informatics approach³⁸ was used to calculate the octanol-water partition coefficient (clog P value) and molecular polar surface area (PSA) for the most active compounds 3a, 3b, 3e, 9m, 9o and 10b, with IC₅₀/24 h in the range of 35.5 to 123 μ M. The clog P and PSA values were in the range of 4.16-4.87 and 28.68-73.46, respectively.

Conclusions

Substituted imidazoles have been synthesized using amidines via a cascade S_N2'-intramolecular aza-Michael addition-elimination with nitroallylic acetates and via a cascade Michael addition-intramolecular S_N2 reaction with α-bromonitroalkenes. Imidazoles belonging to both the series have been screened against T. cruzi bloodstream trypomastigotes, an infective form of the protozoa that causes Chagas disease.

While three of the imidazoles exhibited activity comparable to the effect of the standard compound benznidazole, the activity of two others was two- and three-fold that of the current drug, suggesting possible application of such imidazoles as effective anti-T. cruzi agents.

Experimental section

General

The melting points recorded are uncorrected. NMR spectra (1H, 1H decoupled 13C, 13C-APT and 1H-1H COSY) were recorded with TMS as the internal standard. The coupling constants (I values) are given in Hz. High resolution mass spectra were recorded under ESI Q-TOF conditions. Amidinium salt 2a was purchased from Sigma-Aldrich and others 2b-d were prepared by following published procedures.³⁶ The MBH alcohols and their acetates 1 were prepared by following reported procedures.³⁹ Bromonitroalkenes 8 were prepared by following literature methods. 40 Experimental data for compounds 3a-s, 4d, 5a, 5d, 6a, 6d and 7a were reported in our preliminary communication.26

Trypanocidal assay

Stock solutions of the compounds were prepared in dimethyl sulfoxide (DMSO), with the final concentration of the latter in the experiments never exceeding 0.4%. Preliminary experiments showed that DMSO has no deleterious effect on the parasites when its concentration is up to 4%. T. cruzi bloodstream trypomastigotes (Y strain) were obtained at the peak of parasitaemia from infected albino mice, purified by differential centrifugation and resuspended in RPMI to a parasite concentration of 10⁷ cells per mL in the presence of 10% of mouse blood. This suspension (100 µL) was added into the same volume of each compound previously prepared at twice the desired final concentrations for 24 h at 4 °C. Cell quantification was performed in a Neubauer chamber and the trypanocidal activity was expressed as IC₅₀/24 h, corresponding to the concentration that leads to the lysis of 50% of the parasites. The activity of standard benznidazole was reported earlier.⁴¹ It is different from that reported by Moraes et al.42 due to different experimental conditions.

General procedure for the synthesis of imidazoles from nitroallylic acetates

To a stirred solution of amidine 2 (0.24 mmol) and DABCO (61 mg, 0.5 mmol) in acetonitrile (2 mL), MBH acetate 1 (0.2 mmol) was added. After the completion of the reaction, monitored by TLC, the solvent was removed in vacuo and the crude product was purified by silica gel column chromatography by gradient elution with pet. ether/ethyl acetate (20-70%).

Ethyl 2-(2-(4-chlorophenyl)-4-(3,4-dimethoxyphenyl)-1H-imidazol-5-yl)acetate (3t). Yellow solid; 63%, 50 mg; mp 128 °C; IR (KBr, cm⁻¹) 2963 (m), 2934 (m), 1730 (vs), 1667 (m), 1613 (m), 1593 (m), 1510 (vs), 1481 (s), 1465 (s), 1442 (s), 1254 (vs),

1228 (s), 1176 (s), 1143 (s), 1093 (m), 1027 (vs), 836 (m), 811 (m), 765 (m), 736 (vs); 1 H NMR (CDCl₃, 400 MHz) δ 7.75 (d, J =8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 1.8 Hz, 1H), 6.99 (dd, J = 8.3, 1.8 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); 13 C NMR (CDCl₃, 100 MHz) δ 171.6, 149.1, 148.6, 144.7, 134.5, 129.0, 128.3, 126.7, 124.7, 119.8, 111.3, 110.9, 61.6, 56.0, 55.9, 32.7, 14.3; MS (ES⁺, Ar) m/z (rel. intensity) 403 ([MH + 2]⁺, 33), 401 (M⁺, 100), 248 (15), 110 (25); HRMS (ES⁺, Ar) calcd for C₂₁H₂₂ClN₂O₄ (MH⁺) 401.1263, found 401.1269.

Ethyl 2-(2-(3-chlorophenyl)-4-(3,4-dimethoxyphenyl)-1Himidazol-5-yl)acetate (3u). Yellow solid; yield 67%, 54 mg; mp 126 °C; IR (KBr, cm⁻¹) 2961 (w), 2935 (w), 2838 (w), 1732 (s), 1593 (m), 1510 (s), 1465 (s), 1453 (m), 1320 (w), 1254 (vs), 1227 (s), 1175 (s), 1142 (s), 1026 (s), 865 (w), 737 (vs); ¹H NMR $(CDCl_3, 400 \text{ MHz}) \delta 7.78 \text{ (s, 1H)}, 7.67 \text{ (td, } J = 4.4, 1.6 \text{ Hz, 1H)},$ 7.23-7.26 (m, 2H), 7.11 (d, J = 1.6 Hz, 1H), 6.98 (dd, J = 8.3, 1.6 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.78 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H); 13 C NMR (CDCl₃, 100 MHz) δ 171.6, 149.1, 148.6, 144.3, 134.9, 131.5, 130.2, 128.7, 125.4, 123.5, 119.8, 111.3, 110.8, 61.7, 56.0, 56.0, 32.7, 14.3; MS (ES⁺, Ar) m/z (rel. intensity) 403 ([MH + 2]⁺, 33), 401 (MH⁺, 100), HRMS (ES⁺, Ar) calcd for C₂₁H₂₂ClN₂O₄ (MH⁺) 401.1263, found 401.1261.

Ethyl 2-(4-(3,4-dimethoxyphenyl)-2-p-tolyl-1H-imidazol-5-yl)acetate (3v). Light yellow liquid; yield 63%, 48 mg; IR (neat, cm⁻¹) 2957 (m), 2925 (m), 2853 (w), 1732 (vs), 1614 (m), 1596 (m), 1514 (s), 1464 (m), 1300 (m), 1255 (vs), 1229 (s), 1174 (m), 1142 (m), 1026 (vs), 825 (m), 733 (m); ¹H NMR (CDCl₃, 400 MHz) δ 7.74 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 1.9 Hz, 1H), 7.17 (d, J = 8.2 Hz, 2H), 7.04 (dd, J = 8.3, 1.9 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H, 4.17 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3Hz)3H), 3.78 (s, 2H), 2.34 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 171.5, 149.2, 148.5, 145.9, 138.8, 129.7, 127.2, 125.4, 119.8, 111.4, 111.0, 61.5, 56.1, 56.0, 32.5, 21.5, 14.3; MS (ES⁺, Ar) m/z (rel. intensity) 381 (MH⁺, 100), 349 (5), 320 (10), 301 (8); HRMS (ES⁺, Ar) calcd for C₂₂H₂₅N₂O₄ (MH⁺) 381.1809, found 381.1810.

2-(4-(4-Methoxyphenyl)-2-phenyl-1H-imidazol-5-yl)ethan-1-ol (4a). To a stirred suspension of LAH (16 mg, 0.4 mmol) in THF (3 mL) at 0 °C, was added slowly a solution of ester 3 (70 mg, 0.2 mmol) in THF (1 mL). The reaction mixture was allowed to warm to ambient temperature and stirred for an additional 12 h. After the completion of the reaction (monitored by TLC), a saturated solution of NH₄Cl (5 mL) was added, the resulting mixture was filtered through a pad of celite and the filtrate was concentrated. To the aqueous layer was added ethyl acetate (10 mL), the layers were separated and the organic phase was washed with brine (3 × 5 mL) and water (3 × 5 mL) and dried over anhyd. Na₂SO₄. The combined organic layers were concentrated in vacuo and the residue was subjected to silica gel column chromatography (72% EtOAc/ pet. ether). Colorless solid; yield 76%, 45 mg; mp 196-198 °C; IR (KBr, cm⁻¹) 3397 (br vs), 2925 (w), 1613 (m), 1508 (s), 1463 (m), 1248 (vs), 1177 (m), 1032 (s), 831 (w), 757 (w), 696 (w); ¹H NMR (CDCl₃ + MeOH 3: 1, 400 MHz) δ 7.78 (d, J = 7.9 Hz, 2H),

7.39 (d, J = 8.7 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.23–7.27 (m, 1H), 6.87 (d, J = 8.7 Hz, 2H), 3.75–3.75 (m, 2H), 3.74 (s, 3H), 2.87 (t, J = 6.5 Hz, 2H); ¹³C NMR (CDCl₃ + MeOH 3:1, 100 MHz) δ 158.9, 145.2, 133.0, 130.0, 129.4, 128.8 (×2), 125.4, 124.6, 114.1, 61.8, 55.3, 28.9; MS (ES⁺, Ar) m/z (rel. intensity) 317 (MNa⁺, 50), 295 (MH⁺, 100); HRMS (ES⁺, Ar) calcd for $C_{18}H_{19}N_2O_2$ (MH⁺) 295.1441, found 295.1441.

5-(2-Azidoethyl)-4-(4-methoxyphenyl)-2-phenyl-1H-imidazole (7a). To a stirred solution of imidazolyl alcohol 4a (147 mg, 0.5 mmol) in dry CH₂Cl₂ (10 mL) triethylamine (0.21 mL, 152 mg, 1.5 mmol, 3 equiv.) was added at 0 °C, followed by mesyl chloride (0.12 mL, 172 mg, 1.5 mmol, 3 equiv.). The resulting reaction mixture was stirred for 1 h at 0 °C and then for an additional 2 h at room temperature. After the completion of the reaction, the reaction mixture was diluted with water (10 mL), extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic layers were thoroughly washed with water (3 × 10 mL) to remove the excess mesyl chloride followed by saturated NaHCO₃ (3 \times 10 mL) and 5% dil. HCl (3 \times 10 mL). The organic layer was dried over anhyd. Na2SO4 and concentrated in vacuo. The crude mesylate was suspended in DMF (8 mL) to which NaN₃ (130 mg, 2 mmol, 4 equiv.) was added followed by TBAB (16 mg, 0.05 mmol, 10 mol%). Then the reaction mixture was heated at 90 °C for 12 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were concentrated in vacuo and the residue was purified by silica gel column chromatography to afford diazide 7a as colorless oil; yield 60%, 95 mg; IR (neat, cm⁻¹) 2933 (br m), 2101 (m), 1616 (w), 1507 (s), 1462 (m), 1286 (m), 1250 (vs), 1177 (m), 1029 (w), 912 (w), 835 (m), 735 (m); ¹H NMR (CDCl₃ + MeOH, 500 MHz) δ 7.83 (d, J = 7.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 7.29–7.36 (m, 3H), 6.90 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 3.52 (t, J = 7.0 Hz, 2H), 2.92 (t, J = 7.0 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 159.1, 145.9, 130.2, 128.9 (×2), 128.7, 125.4, 114.3, 55.5, 51.1, 26.7; MS (ES⁺, Ar) m/z (rel. intensity) 320 (MH⁺, 100); HRMS (ES^+, Ar) calcd for $C_{18}H_{18}N_5O(MH^+)$ 320.1506, found 320.1515.

General procedure for the synthesis of imidazoles 9 and 10 from α -bromonitroalkenes 8 and amidines 2

To a stirred solution of α -bromonitroalkene 8 (0.2 mmol) in CH₃CN (3 mL), was added benzamidine hydrochloride 2 (0.2 mmol) followed by Cs₂CO₃ (195 mg, 0.6 mmol) at room temperature. The stirring was continued at room temperature and the completion of the reaction was monitored by TLC analysis. The crude reaction mixture was directly subjected to silica gel column chromatography by eluting with 15–50% EtOAc–pet. ether (gradient elution).

4-(4-Methoxyphenyl)-2-phenyl-1*H***-imidazole** (9a).²⁷ White solid; Yield 93%, 47 mg; mp 175–177 °C (lit²⁷ 178–179 °C); IR (KBr, cm⁻¹) 3161 (w), 2928 (w), 2836 (w), 1607 (w), 1500 (s), 1462 (w), 1249 (vs), 1180 (m), 1030 (m), 835 (m), 694 (m); ¹H NMR (400 MHz, DMSO-d₆) δ 8.02 (d, J = 7.1 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.47–7.45 (m, 2H), 7.37–7.35 (m, 1H), 6.97 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.9, 147.2, 138.6, 130.1, 128.9, 128.7,

126.5, 125.7, 125.3, 117.3, 114.3, 55.4; MS (ES $^+$, Ar) m/z (rel. intensity) 273 (MNa $^+$, 14), 251 (MH $^+$, 100), 132 (10); HRMS (ES $^+$, Ar) calcd for $C_{16}H_{15}N_2O$ (MH $^+$) 251.1179, found 251.1180. The experimental data are consistent with those reported in the literature. ²⁷

4-(3,4-Dimethoxyphenyl)-2-phenyl-1*H*-imidazole (9b). ²⁸ Off white solid; Yield 92%, 52 mg; mp 89–91 °C; IR (neat, cm⁻¹) 3320 (w), 2933 (w), 2837 (w), 1591 (w), 1528 (w), 1506 (vs), 1464 (m), 1252 (vs), 1223 (m), 1142 (m), 1025 (s), 856 (w), 765 (w);

¹H NMR (400 MHz, CDCl₃) δ 7.87 (dd, J = 8.4, 2.8 Hz, 2H), 7.35 (s, 1H), 7.21–7.28 (m, 5H), 6.81 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H);

¹³C NMR (100 MHz, CDCl₃) δ 149.1, 148.2, 147.4, 138.9, 130.2, 128.8, 128.7, 125.8, 125.7, 117.7, 117.5, 111.6, 108.7, 55.9, 55.7; MS (ES⁺, Ar) m/z (rel. intensity) 303 (MNa⁺, 08), 282 (14), 281 (MH⁺, 100); HRMS (ES⁺, Ar) calcd for C₁₇H₁₇N₂O₂ (MH⁺) 281.1285, found 281.1287. Reported only in the patent literature. ²⁸ No experimental data are available.

4-(Benzo[*d*][1,3]dioxol-5-yl)-2-phenyl-1*H*-imidazole (9c). ²⁸ White solid; Yield 90%, 48 mg; mp 156–158 °C; IR (KBr, cm⁻¹) 3402 (br, m), 2892 (w), 1644 (m), 1486 (s), 1233 (vs), 1111 (w), 1039 (s), 936 (w); ¹H NMR (500 MHz, CD₃CN) δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.39–7.37 (m, 2H), 7.35–7.32 (m, 2H), 6.88 (d, *J* = 8.4 Hz, 1H), 5.98 (s, 2H); ¹³C NMR (126 MHz, CD₃CN) δ 149.1, 147.6, 147.4, 140.8, 131.5, 129.8, 129.4, 129.2, 126.2, 119.2, 116.5, 109.4, 106.3, 102.3; MS (ES⁺, Ar) *m/z* (rel. intensity) 287 (MNa⁺, 08), 265 (MH⁺, 100); HRMS (ES⁺, Ar) calcd for C₁₆H₁₃N₂O₂ (MH⁺) 265.0972, found 265.0973. Reported only in the patent literature. ²⁸ No experimental data are available.

2,4-Diphenyl-1*H***-imidazole** (**9d**). ^{27a} White solid; Yield 88%, 39 mg; mp 275–277 °C (lit^{27a} 274–275 °C); IR (KBr, cm⁻¹) 3378 (vs), 2923 (vw), 1640 (s), 1490 (vw), 1460 (vw), 1020 (w), 756 (w), 693 (w); ¹H NMR (400 MHz, CDCl₃) δ 9.30 (br s, 1H), 7.79–7.84 (m, 2H), 7.69 (d, J = 7.4 Hz, 2H), 7.35–7.31 (m, 2H), 7.21–7.29 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 147.6, 138.9, 132.4, 129.8, 129.0, 128.9, 128.8, 127.3, 125.8, 125.2, 118.0; MS (ES⁺, Ar) m/z (rel. intensity) 243 (MNa⁺, 31), 221 (MH⁺, 100); HRMS (ES⁺, Ar) calcd for C₁₅H₁₃N₂ (MH⁺) 221.1073, found 221.1080. The experimental data are consistent with those reported in the literature. ^{27a}

2-Phenyl-4-(*p***-tolyl)-1***H***-imidazole (9e).**²⁹ White solid; Yield 92%, 43 mg; mp 156–159 °C; IR (KBr, cm⁻¹) 3190 (vs), 2920 (m), 2855 (m), 1729 (m), 1661 (w), 1607 (w), 1501 (m), 1460 (s), 1265 (m), 1139 (m), 1020 (w), 953 (w), 821 (s), 775 (s), 694 (s); ¹H NMR (500 MHz, DMSO-d₆) δ 12.60 (br s, 1H), 8.03 (d, J = 7.0 Hz, 2H), 7.75 (d, J = 7.0 Hz, 2H), 7.65 (s, 1H), 7.47 (t, J = 7.1 Hz, 2H), 7.35 (t, J = 7.1 Hz, 1H), 7.20 (d, J = 7.1 Hz, 2H), 2.31 (s, 3H); ¹³C NMR (125 MHz, DMSO-d₆) δ 146.1, 139.7, 135.7, 131.0, 130.7, 129.3, 128.9, 128.3, 125.1, 124.6, 116.2, 20.9; MS (ES⁺, Ar) m/z (rel. intensity) 235 (MH⁺, 100), 121 (3); HRMS (ES⁺, Ar) calcd for C₁₆H₁₅N₂ (MH⁺) 235.1230, found 235.1231. No experimental data are available.²⁹

4-(4-(Methylthio)phenyl)-2-phenyl-1*H*-imidazole (9f).³⁰ White solid; Yield 84%, 45 mg; mp 158–160 °C; IR (KBr, cm⁻¹) 3145 (br, vs), 2916 (br m), 1681 (br m), 1604 (m), 1489 (vs), 1460 (s), 1411 (m), 1297 (w), 1105 (m), 953 (m), 824 (m), 775 (m),

708 (s), 693 (s); 1 H NMR (500 MHz, DMSO-d₆) δ 12.65 (br s, 1H), 8.04 (d, J = 6.9 Hz, 2H), 7.82 (d, J = 7.4 Hz, 2H), 7.71 (s, 1H), 7.48 (t, J = 6.9 Hz, 2H), 7.38 (d, J = 6.9 Hz, 1H), 7.30 (d, J =7.4 Hz, 2H), 2.50 (s, 3H); ¹³C NMR (125 MHz, DMSO-d₆) δ 146.0, 135.6, 130.6, 128.7, 128.1, 126.3, 124.9, 15.0; MS (ES⁺, Ar) m/z (rel. intensity) 289 (MNa⁺, 87), 267 (MH⁺, 100); HRMS (ES^+, Ar) calcd for $C_{16}H_{15}N_2S$ (MH^+) 267.0950, found 267.0950.

(9g).²⁷ White 4-(4-Chlorophenyl)-2-phenyl-1*H*-imidazole solid; Yield 86%, 44 mg; mp 273-275 °C (lit²⁷ 277-280 °C); IR (KBr, cm⁻¹) 3413 (m), 2923 (w), 2852 (w), 1643 (m), 1488 (vs), 1461 (s), 1412 (w), 1265 (m), 1092 (m), 833 (s), 776 (m), 693 (m); ¹H NMR (400 MHz, CDCl₃) δ 8.58 (br s, 1H), 7.75–7.85 (m, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.40–7.20 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 147.9, 139.3, 138.9, 132.7, 131.5, 129.9, 129.1, 129.0, 126.4, 125.8, 117.1; MS (ES⁺, Ar) m/z (rel. intensity) 257 (36), 256 (19), 255 (MH⁺, 100); HRMS (ES⁺, Ar) calcd for $C_{15}H_{12}N_2Cl$ (MH⁺) 255.0684, found 255.0683. The experimental data are consistent with those reported in the literature.²⁷

4-(4-Fluorophenyl)-2-phenyl-1*H*-imidazole (9h).³¹ Pale pink solid; Yield 76%, 36 mg; mp 163-165 °C (lit³¹ 167-168 °C); IR (KBr, cm⁻¹) 3412 (br w), 3069 (br s), 2807 (br m), 1607 (vw), 1497 (s), 1462 (m), 1296 (w), 1231 (s), 1156 (m), 1083 (w), 954 (w), 838 (m), 774 (m), 693 (m); ¹H NMR (500 MHz, CDCl₃) δ 7.82–7.86 (m, 2H), 7.70 (dd, J = 7.7, 5.6 Hz, 2H), 7.33–7.38 (m, 3H), 7.26 (s, 1H), 7.05 (t, J = 8.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 162.2 (d, J = 246.5 Hz), 147.5, 139.3, 130.0, 129.2 (d, I = 3.0 Hz), 129.1, 129.0, 126.9 (d, I = 8.0 Hz), 125.7, 116.1, 115.7 (d, J = 21.1 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -119.2; MS (ES⁺, Ar) m/z (rel. intensity) 261 (MNa⁺, 7), 240 $([M + 2]^+, 15), 239 (MH^+, 100); HRMS (ES^+, Ar) calcd for$ $C_{15}H_{12}FN_2$ (MH⁺) 239.0979, found 239.0979. The experimental data are consistent with those reported in the literature.³¹

4-(3-Bromophenyl)-2-phenyl-1H-imidazole (9i). Greenish liquid; Yield 74%, 44 mg; IR (neat, cm⁻¹) 3063 (br m), 2961 (br m), 2834 (br m), 1604 (w), 1493 (s), 1464 (m), 1247 (vs), 1179 (m), 1080 (w), 1031 (m), 834 (m), 768 (m); ¹H NMR (500 MHz, DMSO-d₆) δ 12.77 (br s, 1H), 8.08 (s, 1H), 8.02 (d, J = 6.4 Hz, 2H), 7.85-7.90 (m, 2H), 7.48 (t, J = 5.9 Hz, 2H), 7.42-7.32 (m, 3H); 13 C NMR (125 MHz, DMSO-d₆) δ 146.4, 139.5, 137.1, 130.6, 130.4, 128.8, 128.7, 128.3, 126.8, 125.1, 123.3, 122.1, 115.4; MS (ES⁺, Ar) m/z (rel. intensity) 301 ([M + 2]⁺, 98), 299 (MH⁺, 100), 251 (53), 185 (25), 153 (29), 129 (47); HRMS (ES⁺, Ar) calcd for C₁₅H₁₂BrN₂ (MH⁺) 299.0178, found 299.0191.

4-(2-Nitrophenyl)-2-phenyl-1*H*-imidazole (9j).³² Yellow solid; Yield 85%, 45 mg; mp 157–159 °C; IR (KBr, cm⁻¹) 3247 (br s), 1612 (vw), 1526 (vs), 1485 (w), 1460 (w), 1366 (s), 1093 (br w), 780 (m), 748 (w), 694 (m); 1 H NMR (500 MHz, CDCl₃) δ 10.18 (br s, 1H), 7.93-7.89 (unresolved m, 1H), 7.83 (d, J = 7.7 Hz, 2H), 7.72 (br d, J = 6.7 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.43-7.36 (m, 4H), 7.31 (s, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ 148.2, 146.3, 136.3, 131.6, 130.2, 129.2, 128.8, 128.5, 127.5, 127.1, 125.0, 123.3, 116.6; MS (ES⁺, Ar) m/z (rel. intensity) 288 $(MNa^+, 54), 267 ([M + 2]^+, 15), 266 (MH^+, 100); HRMS (ES^+, Ar)$ calcd for C₁₅H₁₂N₃O₂ (MH⁺) 266.0924, found 266.0926. Reported only in the patent literature.³² No experimental data are available.

(9k).33 Greenish 2-Phenyl-4-(thiophen-2-yl)-1*H*-imidazole liquid; Yield 85%, 38 mg; IR (neat, cm⁻¹) 3067 (br, m), 2894 (m), 1606 (vw), 1486 (vs), 1343 (vw), 1234 (vs), 1110 (w), 1039 (s), 935 (m), 813 (m), 775 (m), 695 (m); ¹H NMR (500 MHz, CDCl₃) δ 7.85–7.75 (unresolved m, 2H), 7.35–7.27 (unresolved m, 4H), 7.26 (s, 1H), 7.20-7.17 (m, 1H), 7.04-7.00 (unresolved m, 1H); 13 C NMR (126 MHz, CDCl₃) δ 147.5, 136.4, 135.2, 129.9, 129.0, 129.0, 127.8, 125.8, 123.8, 122.8, 116.4; MS (ES⁺, Ar) m/z (rel. intensity) 249 (MNa⁺, 100), 235 (14), 227 (8); HRMS (ES⁺, Ar) calcd for C₁₃H₁₀N₂SNa (MNa⁺) 249.0457, found 249.0456. Experimental data are not available in the literature.

2-Phenyl-4-(thiophen-3-yl)-1*H*-imidazole (9l).³⁴ Off white solid; Yield 71%, 32 mg; mp 146-148 °C (lit³⁴ 151-153 °C); IR (KBr, cm⁻¹) 3067 (br, vs), 2911 (m), 1459 (m), 1423 (m), 1404 (m), 1267 (w), 1212 (w), 1137 (m), 1031 (w), 846 (m), 775 (m), 693 (vs), 667 (m); 1 H NMR (500 MHz, CDCl₃) δ 7.87 (d, J = 7.3 Hz, 2H), 7.67 (s, 1H), 7.48-7.43 (m, 3H), 7.39 (t, J = 1.48 (m, 3H), 7.39 (m, 3H)7.3 Hz, 1H), 7.30 (d, J = 5.7 Hz, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ 145.3, 134.5, 134.2, 130.0, 128.7, 128.4, 128.2, 127.0, 125.2, 117.2, 105.2; MS (ES⁺, Ar) m/z (rel. intensity) 249 (MNa⁺, 9), 241 (13), 227 (MH⁺, 100), 139 (4); HRMS (ES⁺, Ar) calcd for C₁₃H₁₁N₂S (MH⁺) 227.0637, found 227.0637. Only mp and CHN data are reported in the literature.³⁴

4-(Naphthalen-1-yl)-2-phenyl-1H-imidazole (9m). Off white solid; Yield 81%, 44 mg; mp 159–161 °C; IR (KBr, cm⁻¹) 3063 (br, vs), 2918 (s), 1499 (m), 1461 (s), 1414 (w), 1265 (m), 1142 (w), 954 (w), 822 (s), 775 (m), 737 (m), 693 (s); ¹H NMR (500 MHz, CDCl₃) δ 8.34–8.32 (m, 1H), 7.90–7.87 (m, 3H), 7.82 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.53-7.45 (m, 3H),7.40-7.38 (m, 2H), 7.36-7.33 (m, 1H), 7.31 (s, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ 145.8, 138.2, 133.7, 130.9, 130.7, 130.3, 128.9, 128.4, 128.3, 127.5, 126.3, 126.2, 126.1, 125.8, 125.6, 125.2, 119.8; MS (ES⁺, Ar) m/z (rel. intensity) 309 (MK⁺, 26), 293 $(MNa^+, 72), 271 (MH^+, 100); HRMS (ES^+, Ar) calcd for C₁₉H₁₅N₂$ (MH⁺) 271.1230, found 271.1225.

(E)-2-Phenyl-4-styryl-1H-imidazole (9n). Yellow oily liquid; Yield 67%, 33 mg; IR (neat, cm⁻¹) 3203 (br, m), 3066 (m), 2954 (vs), 2926 (vs), 1600 (w), 1485 (m), 1463 (s), 1378 (vw), 1248 (s), 1026 (w), 754 (s), 706 (m); 1 H NMR (500 MHz, CDCl₃) δ 8.81 (br s, 1H), 7.92 (d, J = 6.6 Hz, 2H), 7.33 (d, J = 7.5 Hz, 2H), 7.33-7.25 (m, 5H), 7.16-7.23 (m, 2H), 7.11, 6.98 (ABq, J = 16.4Hz, 2H); 13 C NMR (125 MHz, CDCl₃) δ 147.9, 137.4, 136.1, 129.9, 129.0, 129.0, 128.8, 127.5, 127.5, 126.3, 125.9, 122.7, 117.7; MS (ES⁺, Ar) m/z (rel. intensity) 269 (MNa⁺, 20), 247 (MH⁺, 100); HRMS (ES⁺, Ar) calcd for C₁₇H₁₅N₂ (MH⁺) 247.1230, found 247.1230.

4-Cyclohexyl-2-phenyl-1*H*-imidazole (90).³⁵ Colorless liquid; Yield 85%, 38 mg; IR (neat, cm⁻¹) 3401 (br, m), 2925 (s), 2852 (m), 1644 (w), 1463 (w), 1412 (w), 1266 (w), 1092 (w), 773 (w), 709 (w), 694 (w); ¹H NMR (500 MHz, CDCl₃) δ 7.84–7.82 (m, 2H), 7.32-7.25 (m, 3H), 6.78 (s, 1H), 2.62-2.55 (m, 1H), 2.04-1.97 (m, 2H), 1.78-1.72 (m, 2H), 1.71-1.64 (m, 1H), 1.42–1.16 (m, 5H); 13 C NMR (100 MHz, CDCl₃) δ 145.7, 142.8, 129.8, 129.0, 128.8, 125.6, 118.1, 36.0, 33.1, 26.3, 26.2; MS (ES⁺, Ar) m/z (rel. intensity) 228 ([M + 2]⁺, 15), 227 (MH⁺, 100); HRMS (ES $^+$, Ar) calcd for $C_{15}H_{19}N_2$ (MH $^+$) 227.1543, found 227.1542. No experimental data are available. ³⁵

4-Butyl-2-phenyl-1*H***-imidazole (9p).** Colorless liquid; Yield 75%, 30 mg; IR (neat, cm⁻¹) 3088 (br w), 2900 (w), 1499 (m), 1485 (s), 1460 (m), 1234 (vs), 1127 (m), 1034 (s), 936 (m), 694 (m); ¹H NMR (500 MHz, CDCl₃) δ 8.24 (br s, 1H), 7.85 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 6.82 (s, 1H), 2.59 (t, J = 7.6 Hz, 2H), 1.59 (quint, J = 7.6 Hz, 2H), 1.33 (sextet, J = 7.6 Hz, 2H), 0.87 (t, J = 7.6 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 146.1, 137.9, 130.3, 129.0, 128.5, 125.4, 119.7, 31.6, 26.4, 22.5, 14.0; MS (ES⁺, Ar) m/z (rel. intensity) 202 ([M + 2]⁺, 11), 201 (MH⁺, 100); HRMS (ES⁺, Ar) calcd for $C_{13}H_{17}N_2$ (MH⁺) 201.1386, found 201.1385.

4-(4-Methoxyphenyl)-2-(p-tolyl)-1H-imidazole (10b). Colorless solid; Yield 87%, 46 mg; mp 116–118 °C; IR (KBr, cm⁻¹) 3401 (m), 2928 (s), 2854 (m), 1505 (m), 1441 (m), 1247 (s), 1175 (m), 1143 (m), 1088 (m), 1027 (s), 834 (m), 739 (m); ¹H NMR (400 MHz, DMSO-d₆) δ 8.30 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.52 (s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 3.75 (s, 3H), 2.32 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆) δ 158.0, 145.9, 137.4, 129.3, 128.0, 125.7, 124.9, 114.0, 55.1, 20.9; MS (ES⁺, Ar) m/z (rel. intensity) 287 (MNa⁺, 49), 265 (MH⁺, 100); HRMS (ES⁺, Ar) calcd for $C_{17}H_{17}N_2O$ (MH⁺) 265.1335, found 265.1333.

2-(4-Chlorophenyl)-4-(4-methoxyphenyl)-1*H*-imidazole (10c). ^{15b} Pale yellow solid; Yield 79%, 45 mg; mp 149–151 °C (lit ^{15b} 233–235 °C); IR (KBr, cm⁻¹) 2897 (br s), 1433 (s), 1245 (vs), 1142 (br s), 1026 (s), 835 (m), 738 (s); ¹H NMR (500 MHz, acetone-d₆) δ 8.07 (d, J = 8.5 Hz, 2H), 8.02 (s, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.53 (s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 3.83 (s, 3H); ¹³C NMR (125 MHz, acetone-d₆) δ 158.8, 145.1, 133.2, 129.9, 128.8, 126.6, 125.9, 113.9, 54.6; MS (ES⁺, Ar) m/z (rel. intensity) 307 (MNa⁺, 22), 287 ([M + 2]⁺, 29), 285 (MH⁺, 100); HRMS (ES⁺, Ar) calcd for C₁₆H₁₄ClN₂O (MH⁺) 285.0789, found 285.0788. The experimental data are consistent with those reported in the literature. ^{15b}

2-(3-Chlorophenyl)-4-(4-methoxyphenyl)-1*H*-imidazole (10d). Greenish liquid; Yield 83%, 47 mg; IR (neat, cm $^{-1}$) 3374 (br s), 2834 (m), 1616 (m), 1508 (s), 1393 (vw), 1248 (vs), 1179 (m), 1031 (m), 834 (m); 1 H NMR (500 MHz, CDCl $_{3}$) δ 9.27 (br s, 1H), 7.76 (s, 1H), 7.67–7.65 (m, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.26 (s, 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 6.90 (d, J = 8.6 Hz, 2H), 3.80 (s, 3H); 13 C NMR (125 MHz, CDCl $_{3}$) δ 159.1, 145.9, 139.1, 134.8, 131.7, 130.1, 128.6, 126.6, 125.8, 124.9, 123.8, 117.7, 114.3, 55.5; MS (ES $^{+}$, Ar) m/z (rel. intensity) 286 ([M + 2] $^{+}$, 34), 285 (MH $^{+}$, 100), 129 (41); HRMS (ES $^{+}$, Ar) calcd for $C_{16}H_{14}$ ClN $_{2}$ O (MH $^{+}$) 285.0789, found 285.0798.

4-(4-Methoxyphenyl)-2-(methylthio)-1*H*-imidazole (10e). Yellow oily liquid; Yield 55%, 24 mg; IR (neat, cm $^{-1}$) 3160 (br m), 2955 (br w), 2839 (br m), 1652 (w), 1602 (m), 1507 (m), 1464 (w), 1302 (w), 1250 (vs), 1181 (m), 1030 (m), 834 (m); 1 H NMR (500 MHz, CDCl $_{3}$) δ 8.23 (br s, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.21 (s, 1H), 6.87 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 2.53 (s, 3H); 13 C NMR (125 MHz, CDCl $_{3}$) δ 159.0, 141.9, 139.3, 126.3, 125.2, 117.4, 114.3, 55.4, 17.5; MS (ES $^{+}$, Ar) m/z (rel. intensity)

237 ([MH + H_2O]⁺, 15), 221 (MH⁺, 100); HRMS (ES⁺, Ar) calcd for $C_{11}H_{13}N_2OS$ (MH⁺) 221.0743, found 221.0743.

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