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Double nucleophilic reaction of amines to the imidazole nucleus and selective synthesis of 5-aminoimidazoles

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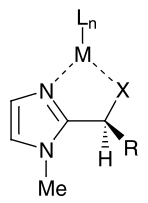
Abstract—Reaction of 2-(1-chloro-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole with an excess of *N*,*N*-dimethylamine at room temperature gave an abnormal adduct, *trans*-4,5-bis(dimethylamino)-1-methyl-2,2-dimethylpropyl-2-imidazoline, which was derived from a serial, double nucleophilic addition into the imidazole nucleus in 74% yield together with a normal S_N product, 1-methyl-2-(1-dimethylamino-2,2-dimethylpropyl)-1*H*-imidazole in 15% yield. The former was easily converted to 1-methyl-5-(dimethylamino)-2-(2,2-dimethylpropyl)-1*H*-imidazole by only reflux in toluene in 90% yield. The scope, mechanism and limitation of these reactions are discussed.

1. Introduction

Electrophilic substitutions of an imidazole nucleus[1] and nucleophilic substitutions via lithioimidazoles[2] have been well known for the preparation of imidazole compounds, and we have applied the reactions of lithioimidazoles[3] and imidazolium salts[4] to the synthesis of several pharmaceutically interesting compounds and natural products.[5] While, nucleophilic reactions to the imidazole ring have been performed mainly through the activation by quaternization of the ring[6] or introduction of an appropriate electron-withdrawing group such as halogen atom(s) into the nucleus,[7] other examples have been quite rare.[8,9] On the other hand, although the structure of 1,2-disubstituted 5-amino-1*H*-imidazole is found in some interesting bioactive compounds such as gonadotropin-releasing hormone receptor antagonists,[10] preparation methods for these aminoimidazole derivatives have been almost unknown in the literature.[11] In this paper, we would like to present a novel, serial double nucleophilic addition of amines into the imidazole nucleus to give 1,2-disubstituted 4,5-bis(amino)-2-imidazolines[9] and the highly regioselective elimination of 2-imidazoline compounds to provide 1,2-disubstituted 5-amino-1*H*-imidazoles.

2. Results and discussion

In the course of our investigations on the synthesis of chiral imidazole bidentate ligands for transition metals as shown in Figure 1, we planned the preparation of 1-methyl-2-(1-aminoalkyl)-1*H*-imidazole, which would be easily derived by a simple S_N2 reaction of an amine with 1-methyl-2-(1-chloroalkyl)-1*H*-imidazole as reported by Miocque.[12] Thus, 1-methyl-2-(1-hydroxy-2,2-dimethylpropyl)-1*H*-imidazole **1a**[13] was chlorinated with thionyl chloride in $CHCl_3$ to give 2-(1-chloro-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole hydrochloride **2a** as colorless crystals in 86% yield. The chloride **2a** was treated with an excess of *N*,*N*-dimethylamine; however, the expected normal S_N product **3a** was obtained in only 15% yield, and the unexpected addition product **4a** was obtained in 74% yield as the major component (Scheme 1, Entry 1 in Table 1). All spectral data of the latter supported the structure of **4a**, and finally it was confirmed by X-ray crystallographic analysis after being derived to the corresponding dipicrate.[9] To our best



X = N, O, P, S....
M = Transition Metal

Figure 1.

Keywords: Imidazoles; Nucleophilic reaction; Stereoselective addition.
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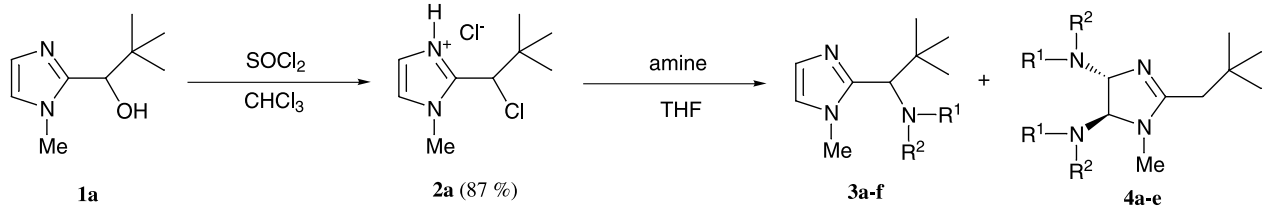


Scheme 1.

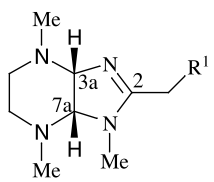
Table 1. Reaction of **2a** with various amines

Entry	Amine	R^1	R^2	Yield (%) (Product)	
				3	**4**
1	Me_2NH	Me	Me	15 (**3a**)	74 (**4a**)
2	Pyrroridine	$-(CH_2)_4-$		6 (**3b**)	68 (**4b**)
3	Piperidine	$-(CH_2)_5-$		13 (**3c**)	61 (**4c**)
4	$BnNH_2$	Bn	H	67 (**3d**)	—[a]
5	$MeNH(CH_2)_2NHMe$	Me	$-(CH)_2NHMe$	—[a]	78 (**4e**)[b]
6	1,2-Diaminobenzene	$2\text{-}NH_2\text{-}C_6H_4$	H	78 (**3f**)	—[a]

[a] Not detected in the reaction mixture.
[b] Obtained product **4e** was the *cis*-isomer shown in Figure 2.

knowledge, this was the first example of direct nucleophilic addition under dearomatizing to the imidazole ring without any electron-withdrawing substituent on the nucleus or through quarternary imidazolium salts.

The reaction of **2a** with various amines was also examined, and the results are shown in Table 1. Reaction of **2a** with secondary amines gave the serial double nucleophilic addition products **4a**–**c** as major products in 61–74% yields (Entries 1–3), whereas the reaction with primary amines gave only S_N products **3d** and **3f** in 67, 78% yields, respectively (Entries 4 and 6). Interestingly, treatment of *N*,*N*′-dimethylethylenediamine provided a bicyclic compound as the sole product, 1*H*-imidazo[4,5-*b*]piperazine **4e** in good yield (78%) (Entry 5, Fig. 2), and its *cis*-fused ring system was confirmed by observation of NOE between H3a and H7a protons and comparison with the ^1H NMR coupling constant of H3a–H7a in the ring (J=8.6 Hz) as these values of H4–H5 in *trans*-4,5-disubstituted 2-imidazolines **4a**–**c** (J=3.8–4.0 Hz).

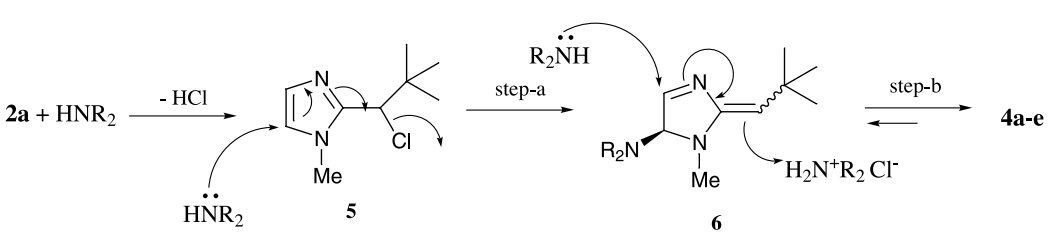


4e R^1 = *t*-Bu
4k R^1 = *i*-Pr

Figure 2.

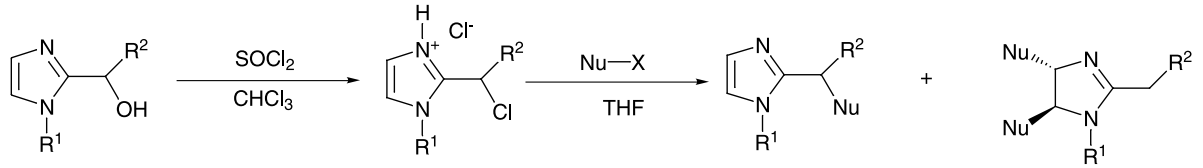
A plausible reaction mechanism for producing the di-adducts **4a**–**e** is given in Scheme 2. The free imidazole **5** reacted with secondary amines at the 5-position of the imidazole ring by a nucleophilic *tele*-substitution reaction mechanism[14] to give the intermediate **6**, and the second molecule of R_2NH might readily add to the unstable ketenediiminal intermediate **6** under assist by protonation with $H_2N^+R_2$ to produce **4**. Main reason for producing the adduct **4** may be difficulty in approach of the amine molecule to the sterically hindered –CHCl– portion where a bulky alkyl group attaches.

Then, the reaction of **2b**–**e** with various nucleophiles was examined, and the results are summarized in Table 2. When compound **2b** (R^2=*i*-Pr) was treated with secondary amines, di-adducts (**4g**–**i**) were obtained in 50–64% overall yield from **1b** (Entries 1–3) together with some S_N products (**3g**–**i**) in 17–19% yield. The treatment with a primary amine gave only S_N product (**3j**) in 36% yield (Entry 4), and *N*,*N*′-dimethylethylenediamine gave bicyclic 1*H*-imidazo[4,5-*b*]piperazine (**4k**) having *cis* stereochemistry in 29% yield (Entry 5, Fig. 2). The reaction showed almost the same tendency as the reaction of **2a** (R^2=*t*-Bu) with amines



Scheme 2.

Table 2. Reaction of **2b**–**e** with various nucleophiles



1b R^1 = Me, R^2 = *i*-Pr
1c R^1 = Me, R^2 = *n*-C_6H_{13}
1d R^1 = Bn, R^2 = *t*-Bu
1e R^1 = H, R^2 = *t*-Bu

2b R^1 = Me, R^2 = *i*-Pr (crude)
2c R^1 = Me, R^2 = *n*-C_6H_{13} (63 %)
2d R^1 = Bn, R^2 = *t*-Bu (73 %)
2e R^1 = H, R^2 = *t*-Bu (crude)

3g-t

4g-q

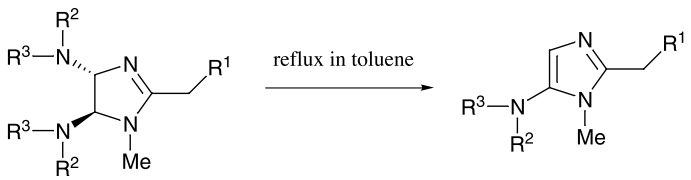
Entry	R^1	R^2	Nu-X	Nu	Yield (%) (Product)	
					3	**4**
1	Me	*i*-Pr	Me_2NH	$-NMe_2$	17 (**3g**)[a]	64 (**4g**)[a]
2	Me	*i*-Pr	Pyrroridine	$-N(CH_2)_4$	19 (**3h**)[a]	50 (**4h**)[a]
3	Me	*i*-Pr	Piperidine	$-N(CH_2)_5$	17 (**3i**)[a]	61 (**4i**)[a]
4	Me	*i*-Pr	$BnNH_2$	–NHBn	36 (**3j**)[a]	—[b]
5	Me	*i*-Pr	$MeNH(CH_2)_2NHMe$	$-NMe(CH_2)_2NMe$	—[b]	29 (**4k**)[a,c]
6	Me	*i*-Pr	PhC(O)SNa	PhC(O)S–	49 (**3l**)[a]	—[b]
7	Me	*n*-C_6H_{13}	Me_2NH	$-NMe_2$	31 (**3m**)	46 (**4m**)
8	Me	*n*-C_6H_{13}	Pyrroridine	$-N(CH_2)_4$	43 (**3n**)	41 (**4n**)
9	Bn	*t*-Bu	Me_2NH	$-NMe_2$	12 (**3p**)	80 (**4p**)
10	Bn	*t*-Bu	Pyrroridine	$-N(CH_2)_4$	18 (**3q**)	72 (**4q**)
11[d]	Bn	*t*-Bu	Me_2CHOH	Me_2CHO-	34 (**3r**)	—[b]
12[d]	Bn	*t*-Bu	PhOH	PhO–	51 (**3s**)	—[b]
13	H	*t*-Bu	Me_2NH	$-NMe_2$	83 (**3t**)[e]	—[b]

[a] Yield from **1b**.
[b] Not detected in the reaction mixture.
[c] Obtained product **4k** was the *cis*-isomer shown in Figure 2.
[d] The reaction was carried out in presence of Et_3N.
[e] Yield from **1e**.

but the ratio of S_N products in Entries 1–3 was slightly increased.

When 2-(1-chloroheptyl)-1-methyl-1*H*-imidazole hydrochloride (**2c**) derived from **1c**[15] bearing a primary alkyl group neighboring the –CHCl– moiety was used as a substrate, double nucleophilic addition products **4m** and **4n** were given in 41–46% yield by the reaction with secondary amines, but the ratio of normal S_N products **3m** and **3n** considerably increased to 31–43% (Entries 7 and 8). The reaction of **2d** (R_1=Bn, R_2=*t*-Bu) with secondary amines gave desired di-adducts **4p** and **4q** in good yields (80, 72%, respectively) as we expected (Entries 9 and 10); however, the reaction of 1-unsubstituted imidazole **2e** afforded only S_N product **3t** in 83% yield (Entry 13). These results might support the steric hindrance around the –CHCl– moiety was one of the important factors for the attack of nucleophiles into the imidazole nucleus as described above. The reaction of **2b** and **2d** with other nucleophiles such as thioate, alcohol and phenol under the same conditions gave only S_N products **3l**, **3r** and **3s** in moderate yields (34–51%) (Entries 6, 11 and 12); these results also

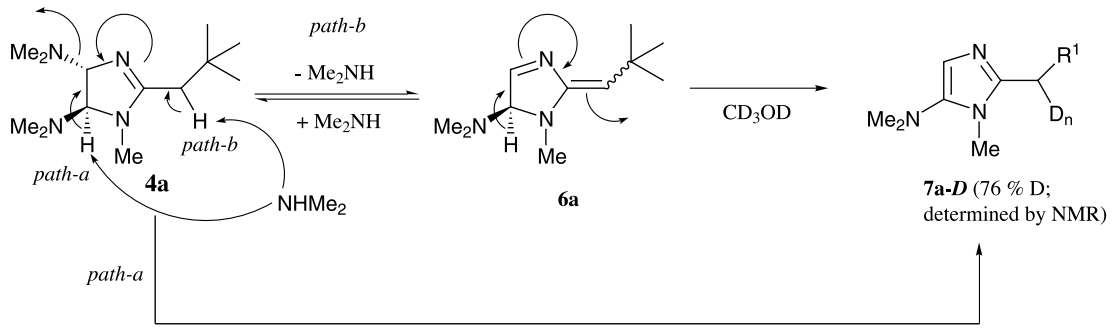
Table 3. Reaction of **4** in reflux toluene



4 **7**

Entry	R^1	**4**	R^2	R^3	Yield (%) (Product)
1	*t*-Bu	**4a**	Me	Me	90 (**7a**)
2	*t*-Bu	**4b**	$-(CH_2)_4-$		83 (**7b**)
3	*t*-Bu	**4e**	[a]		—[b]
4	*i*-Pr	**4g**	Me	Me	66 (**7c**)
5	*i*-Pr	**4h**	$-(CH_2)_4-$		80 (**7d**)

[a] Starting compound was *cis*-isomer **4e** shown in Figure 2.
[b] Not detected in the reaction mixture.



Scheme 3.

showed that one important factor to afford 2-imidazolines **4** was the steric hindrance of nucleophiles as well as their nucleophilicity.

Reaction of double nucleophilic addition products **4a** was examined (Table 3). Regioselective elimination of one of the two *N*,*N*-dimethylamino groups smoothly proceeded in boiling toluene to give 1-methyl-5-dimethylamino-2-(2,2-dimethylpropyl)-1*H*-imidazole **7a** as the sole product in 90% yield (Entry 1). The structure of **7a** was confirmed by the observation of HMBC correlations. Although Stradi reported a conversion of 4,5-diamino-1,2-diaryl-2-imidazolines to 5-amino-1,2-diaryl-1*H*-imidazoles in the presence of triethylamine hydrochloride at 125 °C,[11a] the transformation from **4a** to **7a** could be achieved by only reflux in toluene without any catalyst.

To confirm the reaction mechanism of the selective elimination of **4a**, the reaction was performed in the presence of CD_3OD at 120 °C, and it was found that 76% of deuterium was incorporated into the methylene group of the side chain in the product **7a**–***D***. From this result, we considered that the main reaction course was *path-b* through a *tele*-elimination mechanism[16] as shown in Scheme 3.

This selective elimination reaction was examined toward several 4,5-diaminoimidazoles **4b**, **4e**, **4g** and **4h** and the results are listed in Table 3. The reaction of **4b**, **4g** and **4h** provided the corresponding 1,2-disubstituted 5-amino-1*H*-imidazoles **7b**–**d** in 66–83% yields (Entries 2, 4 and 5). However, the reaction of **4e** mainly recovered the starting compound and gave no desired eliminating product (Entry 3), this result might be explained by the faster intramolecular cyclization of **6e** to **4e** than the approach of the –NHMe portion of **6e** to the sterically hindered H5 for producing **7e** (Scheme 4).

3. Conclusion

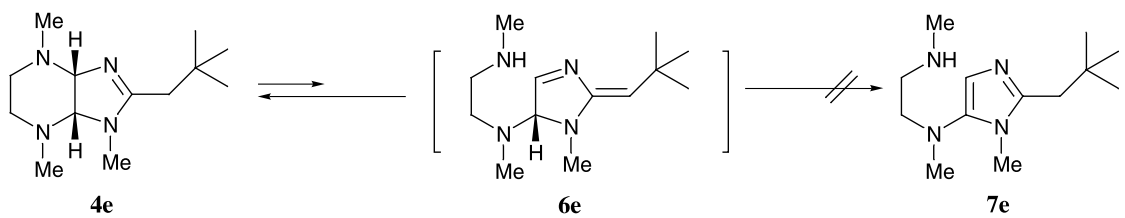
In summary, we have demonstrated a novel dearomatizing reaction of the imidazole ring by the double nucleophilic reaction of amines to give 1,2-dialkyl-4,5-diamino-2-imidazolines and their conversion to 1,2-disubstituted 5-amino-1*H*-imidazoles.

4. Experimental

4.1. General

All melting points were measured with a Yanaco MP micro-melting-point apparatus and are uncorrected. IR spectra were taken with Shimadzu IR-435 spectrophotometer. NMR (^1H and ^{13}C) spectra were measured on Varian UNITY INOVA 400NB (^1H: 400 MHz), JEOL EX-300 (^1H: 300 MHz, ^{13}C: 75 MHz) or JEOL EX-270 (^1H: 270 MHz, ^{13}C: 68 MHz) spectrometer and the chemical shifts were expressed in parts per million downfield from tetramethylsilane as the internal standard. Mass spectra (MS) were measured on JEOL JMS-SX 102A QQ (FAB) or JEOL JMS BU-20 (EI and CI) spectrometer, respectively. Silica gel (Merck Art. 7737) or Al_2O_3 (Nakalai Tesque, Alumina activated 300) was used for column chromatography.

4.1.1. Synthesis of 2-(1-hydroxy-2-methylpropyl)-1-methyl-1*H*-imidazole 1b—general procedure for the synthesis of the alcohols 1. *n*-BuLi (1.6 M in *n*-hexane; 32.8 mL, 52.5 mmol) was added to a stirred solution of 1-methylimidazole (4.4 mL, 55 mmol) in THF (50 mL) under N_2 at −78 °C. After stirring for 30 min at the same temperature, isobutylaldehyde (4.54 mL, 50 mmol) was added and the whole was stirred for 2 h at ambient temperature. The mixture was acidified with HCl aq. (10%, 50 mL) and washed with diethyl ether (30 mL×2).



Scheme 4.

The aqueous layer was basified with K_2CO_3 powder and extracted with AcOEt (30 mL×3). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was recrystallized from AcOEt-*n*-hexane to give **1b** as colorless prisms (3.58 g, 46%). Mp 77–79 °C.

δ_H (300 MHz, $CDCl_3$): 0.81 (3H, d, *J*=6.8 Hz, $CH(CH_3)_2$), 1.06 (3H, d, *J*=6.6 Hz, $CH(CH_3)_2$), 2.06–2.22 (1H, m, $CH(CH_3)_2$), 3.67 (3H, s, NCH_3), 4.25 (1H, br, OH), 4.34 (1H, d, *J*=7.9 Hz, C*H*(OH)), 6.77 (1H, d, *J*=1.1 Hz, Im-H), 6.91 (1H, d, *J*=1.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 18.6, 19.0, 32.9, 33.9, 72.3, 121.0, 126.6, 149.7. ν_{max} ($CHCl_3$, cm^{-1}): 1464, 1489, 2942, 3099. EI MS (*m*/*z*, %): 83 (24), 111 (100), 137 (4), 154 (M^+, 7). HRMS (EI): found M^+ 154.1103, $C_8H_{14}N_2O$ requires M^+ 154.1106. Anal. calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17; found: C, 62.12; H, 9.26; N, 17.95.

The alcohols **1a**[13] and **1c**[15] are known compounds in literature.

4.1.2. 1-Benzyl-2-(1-hydroxy-2,2-dimethylpropyl)-1*H*-imidazole 1d.[17] Obtained, after silica gel column chromatography (AcOEt/*n*-hexane=2:1) and recrystallization from EtOH–Et_2O, as colorless needles (1.98 g, 41%) from 1-benzylimidazole (20 mmol). Mp 113–115 °C.

δ_H (300 MHz, $CDCl_3$): 1.00 (9H, s, $C(CH_3)_3$), 3.08 (1H, br, OH), 4.41 (1H, s, C*H*(OH)), 5.16 (2H, s, NCH_2), 6.76 (1H, d, *J*=1.3 Hz, Im-H), 7.02 (1H, d, *J*=1.3 Hz, Im-H), 7.08–7.11 (2H, m, Ar-H), 7.27–7.37 (3H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 25.8, 37.0, 50.0, 73.8, 119.9, 126.9, 127.5, 128.1, 128.9, 136.3, 149.0. ν_{max} ($CHCl_3$, cm^{-1}): 1449, 1475, 1491, 1622, 2936, 3000–3500. EI MS (*m*/*z*, %): 91 (84), 97 (16), 187 (100), 211 (8), 244 (M^+, 10). HRMS (EI): found M^+ 244.1575, $C_{15}H_{20}N_2O$ requires M^+ 244.1576. Anal. calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47; found: C, 73.49; H, 8.37; N, 11.75.

4.1.3. 2-(1-Hydroxy-2,2-dimethylpropyl)-1*H*-imidazole 1e. Following the reported procedure by Curtis and Brown[18] starting from 1-diethoxymethyl-1*H*-imidazole and trimethylacetaldehyde, the title compound was obtained in 35% yield as colorless prisms, mp 179–181 °C (recrystallized from EtOH–Et_2O).

δ_H (300 MHz, DMSO-d_6): 0.84 (9H, s, $C(CH_3)_3$), 4.24 (1H, d, *J*=4.4 Hz, C*H*(OH)), 5.42 (1H, d, *J*=4.8 Hz, OH), 6.76 (1H, br, Im-H), 6.93 (1H, br, Im-H). δ_C (75 MHz, DMSO-d_6): 26.0, 35.4, 75.1, 115.1, 126.5, 149.4. ν_{max} (KBr, cm^{-1}): 1448, 1639, 2619, 2942, 3163, 3000–3500. EI MS (*m*/*z*, %): 69 (16), 98 (100), 121 (20), 154 (M^+, 8). HRMS (EI): found M^+ 154.1093, $C_8H_{14}N_2O$ requires M^+ 154.1106. Anal. calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17; found: C, 61.92; H, 9.09; N, 17.98.

4.1.4. Synthesis of 2-(1-chloro-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole hydrochloride 2a—general procedure for the synthesis of the chlorides 2. $SOCl_2$ (0.73 mL, 10 mmol) was added to a stirred solution of 2-(1-hydroxy-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole[13] (840 mg, 5 mmol) in $CHCl_3$ (5 mL) under N_2 at 0 °C. After stirring for 2 h at room temperature, solvents were evaporated to give a crystalline residue, which was recrystallized from EtOH–AcOEt. The compound was obtained as a colorless powder, 961 mg (86%). Mp 168–170 °C.

δ_H (300 MHz, CD_3OD): 1.15 (9H, s, $C(CH_3)_3$), 4.00 (3H, s, NCH_3), 5.54 (1H, s, C*H*Cl), 7.62 (1H, d, *J*=2.2 Hz, Im-H), 7.66 (1H, d, *J*=1.8 Hz, Im-H). δ_C (75 MHz, CD_3OD): 26.4, 36.3, 39.7, 59.7, 121.0, 125.4, 145.3. ν_{max} (KBr, cm^{-1}): 1463, 1514, 1591, 2913, 3396. EI MS (*m*/*z*, %): 57 (6), 81 (11), 95 (36), 121 (13), 130 (100), 132 (32), 151 (15), 171 (5), 186 (M^+, 4), 188 (1). HRMS (EI): found M^+ 186.0933, $C_9H_{15}ClN_2$ requires M^+ 186.0924. Anal. calcd for $C_9H_{16}Cl_2N_2$: C, 48.44; H, 7.23; N, 12.55; found: C, 48.51; H, 7.34; N, 12.24.

4.1.5. 2-(1-Chloro-2-methylpropyl)-1-methyl-1*H*-imidazole hydrochloride 2b. Obtained, after evaporation of the solvents from **1b**, as a pale yellow crystalline residue, which was used in the next reaction without further purification.

δ_H (270 MHz, $CDCl_3$): 0.96 (3H, d, *J*=6.6 Hz, $CH(CH_3)_2$), 1.29 (3H, d, *J*=6.4 Hz, $CH(CH_3)_2$), 2.63–2.77 (1H, m, $CH(CH_3)_2$), 4.10 (3H, s, NCH_3), 5.34 (1H, d, *J*=10.2 Hz, C*H*Cl), 7.36 (1H, d, *J*=1.8 Hz, Im-H), 7.63 (1H, d, *J*=1.8 Hz, Im-H). δ_C (68 MHz, $CDCl_3$): 19.8, 20.1, 34.1, 35.8, 55.4, 118.7, 124.2, 143.5. ν_{max} ($CHCl_3$, cm^{-1}): 1464, 1594, 2950, 3138, 3360. EI MS (*m*/*z*, %): 81 (27), 96 (48), 121 (90), 130 (75), 132 (25), 137 (100), 172 (M^+, 10), 174 (3). HRMS (EI): found M^+ 172.0773, $C_8H_{13}ClN_2$ requires M^+ 172.0767.

4.1.6. 2-(1-Chloroheptyl)-1-methyl-1*H*-imidazole hydrochloride 2c. Obtained, after recrystallization from AcOEt–Et_2O, as a colorless powder (478 mg, 63%) from **1c** (3 mmol). Mp 107–111 °C.

δ_H (300 MHz, $CDCl_3$): 0.87 (3H, t, *J*=6.8 Hz, CH_2CH_3), 1.26–1.69 (8H, m, $CH_2(CH_2)_4CH_3$), 2.30–2.51 (2H, m, $CH_2C_5H_{11}$), 4.06 (3H, s, NCH_3), 5.55 (1H, dd, *J*=6.8, 8.8 Hz, C*H*Cl), 7.35 (1H, d, *J*=1.8 Hz, Im-H), 7.47 (1H, d, *J*=1.6 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 13.9, 22.4, 26.5, 28.2, 31.4, 35.3, 35.5, 49.0, 119.1, 124.0, 143.8. ν_{max} ($CHCl_3$, cm^{-1}): 1458, 1518, 1593, 1842, 2422, 2936. EI MS (*m*/*z*, %): 109 (45), 130 (100), 135 (32), 179 (53), 185 (14), 214 (M^+, 5), 216 (2). HRMS (EI): found M^+ 214.1251, $C_{11}H_{19}ClN_2$ requires M^+ 214.1237. Anal. calcd for $C_{11}H_{20}Cl_2N_2$: C, 52.60; H, 8.03; N, 11.15; found: C, 52.28; H, 8.02; N, 11.11.

4.1.7. 1-Benzyl-2-(1-chloro-2,2-dimethylpropyl)-1*H*-imidazole hydrochloride 2d. Obtained, after recrystallization from EtOH–Et_2O as a colorless powder (218 mg, 73%) from **1d** (1 mmol). Mp 151–152 °C.

δ_H (300 MHz, DMSO-d_6): 1.07 (9H, s, $C(CH_3)_3$), 5.53 and 5.725 (1H each, each d, *J*=15.4 Hz, NCH_2), 5.733 (1H, s, C*H*Cl), 7.29–7.80 (7H, m, Ar-H and Im-H). δ_C (75 MHz, DMSO-d_6): 25.9, 37.7, 50.4, 58.4, 121.9, 122.9, 127.6, 128.5, 129.0, 134.9, 142.9. ν_{max} (KBr, cm^{-1}): 1462, 1502, 1598, 1626, 2638, 3394. EI MS (*m*/*z*, %): 91 (100), 115 (30), 171 (90), 206 (50), 262 (M^+, 18), 264 (6). HRMS (EI): found M^+ 262.1223, $C_{15}H_{19}ClN_2$ requires M^+ 262.1237.

Anal. calcd for $C_{15}H_{20}Cl_2N_2$: C, 60.21; H, 6.74; N, 9.36; found: C, 60.35; H, 7.05; N, 8.99.

4.1.8. 2-(1-Chloro-2,2-dimethylpropyl)-1*H*-imidazole hydrochloride 2e. Obtained, after evaporation of the solvents from **1e**, as a pale yellow crystalline residue, which was used in the next reaction without further purification.

4.1.9. Synthesis of 1-methyl-2-(2,2-dimethyl-1-dimethylaminopropyl)-1*H*-imidazole 3a and (4*R,5*R**)-4,5-dihydro-1-methyl-4,5-bis(dimethylamino)-2-(2,2-dimethylpropyl)-1*H*-imidazole 4a—general procedure for the synthesis of 3 and 4 (Entry 1 in Table 1 as an example).** *N*,*N*-Dimethylamine aqueous solution (3 mL, 33 mmol) was added to a suspension of **2a** (669 mg, 3 mmol) in THF (3 mL) under N_2 and ice cooling, and the mixture was stirred for 4 h at 0 °C. 10% K_2CO_3 aqueous solution (5 mL) was added to the reaction mixture and the products were extracted with AcOEt (10 mL×3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated to give an oily residue, which was separated by Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:1 to AcOEt only) to give **3a** (first fraction, 88 mg, 15%) and **4a** (second fraction, 534 mg, 74%) as a yellow viscous oil, respectively.

3a: δ_H (400 MHz, $CDCl_3$): 1.06 (9H, s, $C(CH_3)_3$), 2.34 (6H, s, $N(CH_3)_2$), 3.38 (1H, s, $CHC(CH_3)_3$), 3.64 (3H, s, NCH_3), 6.81 (1H, d, J=1.3 Hz, Im-H), 7.05 (1H, d, J=1.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 27.9, 33.4, 36.9, 44.7, 67.3, 120.0, 126.8, 145.4. ν_{max} ($CHCl_3$, cm^{-1}): 1477, 2956. EI MS (*m*/*z*, %): 110 (57), 138 (100), 195 (M^+, 6). HRMS (EI): found M^+ 195.1732, $C_{11}H_{21}N_3$ requires M^+ 195.1735.

4a: δ_H (400 MHz, $CDCl_3$): 1.08 (9H, s, $C(CH_3)_3$), 2.24 (6H, s, $N(CH_3)_2$), 2.30 (6H, s, $N(CH_3)_2$), 2.21 (1H, d, J=13.6 Hz, $CH_2C(CH_3)_3$), 2.26 (1H, d, J=13.7 Hz, $CH_2C(CH_3)_3$, 2.90 (3H, s, NCH_3), 3.96 (1H, d, J=3.8 Hz, Im-H), 4.25 (1H, d, J=3.8 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 29.9, 31.4, 31.9, 38.4, 40.0, 40.1, 82.8, 85.5, 164.7. ν_{max} ($CHCl_3$, cm^{-1}): 1464, 1586, 2920. EI MS (*m*/*z*, %): 138 (100), 195 (31), 240 (M^+, 1.7). HRMS (EI): found M^+ 240.2309, $C_{13}H_{28}N_4$ requires M^+ 240.2314.

4.1.10. 2-[2,2-Dimethyl-1-(1-pyrrolidinyl)propyl]-1-methyl-1*H*-imidazole 3b and (4*R,5*R**)-4,5-dihydro-1-methyl-2-(2,2-dimethylpropyl)-4,5-bis(1-pyrrolidinyl)-1*H*-imidazole 4b.** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:5 to AcOEt only), as a yellow viscous oil [(**3b**; 14 mg, 6%), (**4b**; 199 mg, 68%)] from pyrrolidine (5 mmol) and **2a** (1 mmol).

3b: δ_H (400 MHz, $CDCl_3$): 1.05 (9H, s, $C(CH_3)_3$), 1.61–1.68 (4H, m, $NCH_2(CH_2)_2$), 2.56–2.58 (2H, m, NCH_2CH_2), 2.82 (2H, br, NCH_2CH_2), 3.62 (1H, s, $CHC(CH_3)_3$), 3.64 (3H, s, NCH_3), 6.78 (1H, d, J=1.1 Hz, Im-H,), 7.03 (1H, d, J=1.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 23.6, 28.2, 33.3, 36.8, 52.0, 65.1, 119.7, 126.8, 147.1. ν_{max} ($CHCl_3$, cm^{-1}): 1477, 2934. HRMS (FAB+): found MH^+ 222.1977, $C_{13}H_{23}N_3$+H requires MH^+ 222.1970.

4b: δ_H (300 MHz, $CDCl_3$): 1.07 (9H, s, $C(CH_3)_3$), 1.71–1.81 (8H, m, NCH_2CH_2), 2.22 (2H, s, $CH_2C(CH_3)_3$), 2.59–2.78 (8H, m, NCH_2CH_2), 2.90 (3H, s, NCH_3), 4.29 (1H, d, J=3.8 Hz, Im-H), 4.36 (1H, d, J=3.8 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 23.4, 23.7, 30.0, 31.5, 33.0, 40.3, 46.7, 48.2, 82.3, 82.7, 164.9. ν_{max} ($CHCl_3$, cm^{-1}): 1585, 2912. EI MS (*m*/*z*, %): 83 (100), 111 (27), 164 (86), 221 (23), 292 (M^+, 9). HRMS (EI): found M^+ 292.2621, $C_{17}H_{32}N_4$ requires M^+ 292.2627.

4.1.11. 2-[2,2-Dimethyl-1-(1-piperidinyl)propyl]-1-methyl-1*H*-imidazole 3c and (4*R,5*R**)-4,5-dihydro-1-methyl-2-(2,2-dimethylpropyl)-4,5-bis(1-piperidinyl)-1*H*-imidazole 4c.** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:2 to AcOEt only), as a yellow viscous oil [(**3c**; 63 mg, 13%), (**4c**; 389 mg, 61%)] from piperidine (10 mmol) and **2a** (2 mmol).

3c: δ_H (300 MHz, $CDCl_3$): 1.04 (9H, s, $C(CH_3)_3$), 1.24–1.35 (2H, m, $NCH_2CH_2CH_2$), 1.46–1.53 (4H, m, NCH_2CH_2), 2.11–2.41 (2H, m, NCH_2CH_2), 2.67–2.96 (2H, m, NCH_2CH_2), 3.28 (1H, s, $CHC(CH_3)_3$), 3.63 (3H, s, NCH_3), 6.79 (1H, d, J=1.1 Hz, Im-H), 7.02 (1H, d, J=1.3 Hz, Im-H,). δ_C (75 MHz, $CDCl_3$): 24.4, 26.8, 27.5, 33.4, 37.2, 54.4, 68.1, 119.8, 126.5, 146.4. ν_{max} ($CHCl_3$, cm^{-1}): 1478, 1655, 2917. HRMS (FAB+): found MH^+ 236.2123, $C_{14}H_{25}N_3$+H requires MH^+ 236.2127.

4c: δ_H (300 MHz, $CDCl_3$): 1.06 (9H, s, $C(CH_3)_3$), 1.42–1.60 (12H, m, $NCH_2(CH_2)_3$), 2.18 and 2.24 (1H each, each d, J=13.6 Hz, $CH_2C(CH_3)_3$), 2.45–2.60 (8H, m, NCH_2CH_2), 2.87 (3H, s, NCH_3), 3.95 (1H, d, J=4.0 Hz, Im-H), 4.24 (1H, d, J=3.9 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 24.7, 24.8, 26.16, 26.22, 30.1, 31.6, 32.7, 40.3, 48.4, 49.3, 85.0, 86.0, 164.7. ν_{max} ($CHCl_3$, cm^{-1}): 1590, 2843. HRMS (FAB+): found MH^+ 321.3026, $C_{19}H_{36}N_4$+H requires MH^+ 321.3018.

4.1.12. 2-(1-Benzylamino-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole 3d. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=2:1 to AcOEt only), as a yellow viscous oil (347 mg, 67%) from benzylamine (10 mmol) and **2a** (2 mmol).

δ_H (300 MHz, $CDCl_3$): 0.96 (9H, s, $C(CH_3)_3$), 2.37 (1H, br, NH), 3.27–3.31 (2H, overlap, $CHC(CH_3)_3$ and NCH_2), 3.35 (3H, s, NCH_3), 3.76 (1H, d, J=13.6 Hz, NCH_2), 6.74 (1H, d, J=1.1 Hz, Im-H), 7.04 (1H, d, J=1.1 Hz, Im-H), 7.18–7.30 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 26.6, 32.6, 36.0, 51.9, 60.7, 119.8, 126.6, 127.1, 128.0, 128.1, 140.2, 149.5. ν_{max} ($CHCl_3$, cm^{-1}): 1478, 1598, 2936, 3156. EI MS (*m*/*z*, %): 65 (17), 91 (38), 152 (11), 200 (100), 257 (M^+, 1). HRMS (EI): found M^+ 257.1887, $C_{16}H_{23}N_3$ requires M^+ 257.1892.

4.1.13. (3*aR,7*aS**)-3a,4,5,6,7,7a-Hexahydro-1,4,7-trimethyl-2-(2,2-dimethylpropyl)-1*H*-imidazo[4,5-*b*]pyrazine 4e.** Obtained, after Al_2O_3 column chromatography (AcOEt only to AcOEt/MeOH=10:1), as a yellow viscous oil (372 mg, 78%) from *N*,*N*′-dimethylethylenediamine (10 mmol) and **2a** (2 mmol).

δ_H (300 MHz, $CDCl_3$): 1.08 (9H, s, $C(CH_3)_3$), 2.15 and 2.23 (1H each, each d, J=13.4 Hz, $CH_2C(CH_3)_3$), 2.49 (3H, s, CH_2NCH_3), 2.57 (3H, s, CH_2NCH_3), 2.52–2.80 (4H, m,

CH_2CH_2), 2.87 (3H, s, NCH_3), 4.17 (1H, d, J=8.6 Hz, Im-H), 4.55 (1H, d, J=8.6 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 29.9, 31.4, 34.1, 40.5, 42.1, 42.9, 44.7, 45.5, 79.5, 81.1, 166.5. ν_{max} ($CHCl_3$, cm^{-1}): 1461, 1590, 2899. EI MS (*m*/*z*, %): 96 (47), 99 (27), 112 (55), 126 (34), 153 (100), 182 (15), 238 (M^+, 20). HRMS (EI): found M^+ 238.2153, $C_{13}H_{26}N_4$ requires M^+ 238.2157.

4.1.14. 2-[1-(2-Aminophenylamino)-2,2-dimethylpropyl]-1-methyl-1*H*-imidazole 3f. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:3), as a solid (403 mg, 78%) from *o*-phenylenediamine (10 mmol) and **2a** (2 mmol).

δ_H (300 MHz, $CDCl_3$): 1.12 (9H, s, $C(CH_3)_3$), 3.44 (3H, s, NCH_3), 3.58–3.77 (2H, br, NH_2), 3.99 (1H, d, J=10.3 Hz, NH), 4.09 (1H, d, J=9.5 Hz,, C*H*C$(CH_3)_3$), 6.49–6.71 (5H, m, Ar-H and Im-H), 6.97 (1H, d, J=1.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 26.7, 32.9, 36.7, 60.2, 116.4, 118.0, 119.7, 120.0, 121.2, 127.0, 136.4, 137.7, 149.5. ν_{max} ($CHCl_3$, cm^{-1}): 1497, 1608, 2936, 3186, 3381. EI MS (*m*/*z*, %): 83 (100), 119 (34), 201 (13), 258 (M^+, 10). HRMS (EI): found M^+ 258.1848, $C_{15}H_{22}N_4$ requires M^+ 258.1844.

4.1.15. 1-Methyl-2-(2-methyl-1-dimethylaminopropyl)-1*H*-imidazole 3g and (4*R,5*R**)-4,5-dihydro-1-methyl-4,5-bis(dimethylamino)-2-(2-methylpropyl)-1*H*-imidazole 4g.** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:1 to AcOEt/MeOH=10:1), as a yellow viscous oil [(**3g**; 155 mg, 17%), (**4g**; 723 mg, 64%)] from crude **2b** (starting from 5 mmol of **1b**).

3g: δ_H (300 MHz, $CDCl_3$): 0.68 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.08 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 2.24 (6H, s, $N(CH_3)_2$), 2.32–2.46 (1H, m, –C*H*$(CH_3)_2$), 3.24 (1H, d, J=9.9 Hz, C*H*$CH(CH_3)_2$), 3.65 (3H, s, NCH_3), 6.79 (1H, d, J=1.1 Hz, Im-H,), 7.02 (1H, d, J=1.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 19.7, 20.1, 29.8, 32.6, 41.1, 65.7, 119.8, 126.8, 146.2. ν_{max} ($CHCl_3$, cm^{-1}): 1479, 2924. EI MS (*m*/*z*, %): 97 (14), 123 (24), 138 (100), 181 (M^+, 1). HRMS (EI): found M^+ 181.1591, $C_{10}H_{19}N_3$ requires M^+ 181.1579.

4g: δ_H (300 MHz, $CDCl_3$): 0.94 (3H, d, J=5.7 Hz, $CH(CH_3)_2$), 0.95 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), 1.93–2.25 (3H, m, $CH_2CH(CH_3)_2$), 2.15 (6H, s, $N(CH_3)_2$), 2.21 (6H, s, $N(CH_3)_2$), 2.82 (3H, s, NCH_3), 3.89 (1H, d, J=3.7 Hz, Im-H), 4.14 (1H, d, J=3.7 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 22.2, 22.8, 26.3, 30.9, 36.5, 38.2, 39.8, 82.7, 85.4, 165.5. ν_{max} ($CHCl_3$, cm^{-1}): 1594, 2933. EI MS (*m*/*z*, %): 91 (62), 138 (58), 181 (37), 205 (100), 226 (M^+, 12). HRMS (EI): found M^+ 226.2153, $C_{12}H_{26}N_4$ requires M^+ 226.2157.

4.1.16. 1-Methyl-2-[2-methyl-1-(1-pyrrolidinyl)propyl]-1*H*-imidazole 3h and (4*R,5*R**)-4,5-dihydro-1-methyl-2-(2-methylpropyl)-4,5-bis(1-pyrrolidinyl)-1*H*-imidazole 4h.** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:5 to AcOEt/MeOH=10:1), as a yellow viscous oil [(**3h**; 118 mg, 19%), (**4h**; 418 mg, 50%)] from pyrrolidine (15 mmol) and crude **2b** (starting from 3 mmol of **1b**).

3h: δ_H (300 MHz, $CDCl_3$): 0.79 (3H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.02 (3H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.60–1.78 (4H, m, NCH_2CH_2), 2.26–2.41 (3H, m, NCH_2CH_2 and $CH(CH_3)_2$), 2.70–2.77 (2H, m, NCH_2CH_2), 3.48 (1H, d, J=8.4 Hz, C*H*C$H(CH_3)_2$), 3.68 (3H, s, NCH_3), 6.78 (1H, d, J=1.1 Hz, Im-H), 7.00 (1H, d, J=1.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 19.1, 20.5, 23.0, 31.3, 32.9, 49.6, 64.1, 120.1, 127.0, 146.9. ν_{max} ($CHCl_3$, cm^{-1}): 1478, 1657, 2924. EI MS (*m*/*z*, %): 123 (93), 138 (100), 164 (99), 207 (M^+, 1). HRMS (EI): found M^+ 207.1737, $C_{12}H_{21}N_3$ requires M^+ 207.1735.

4h: δ_H (300 MHz, $CDCl_3$): 0.91 (3H, d, J=6.2 Hz, $CH(CH_3)_2$), 0.92 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.62–1.72 (8H, m, NCH_2CH_2), 1.86–2.15 (3H, m, CH_2-C*H*C$(CH_3)_2$), 2.49–2.69 (8H, m, NCH_2CH_2), 2.82 (3H, s, NCH_3), 4.22 (1H, d, J=3.3 Hz, Im-H), 4.25 (1H, d, J=3.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 22.3, 22.9, 23.2, 23.7, 26.4, 31.7, 36.6, 46.5, 48.4, 82.2, 82.4, 165.8. ν_{max} ($CHCl_3$, cm^{-1}): 1460, 1592, 2934. EI MS (*m*/*z*, %): 164 (100), 179 (7), 207 (28), 263 (5), 278 (M^+, 5). HRMS (EI): found M^+ 278.2478, $C_{16}H_{30}N_4$ requires M^+ 278.2470.

4.1.17. 1-Methyl-2-[2-methyl-1-(1-piperidinyl)propyl]-1*H*-imidazole (3i) and (4*R,5*R**)-4,5-dihydro-1-methyl-2-(2-methylpropyl)-4,5-bis(1-piperidinyl)-1*H*-imidazole (4i).** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:5), as a yellow viscous oil [(**3i**; 115 mg, 17%), (**4i**; 562 mg, 61%) from piperidine (15 mmol)] and crude **2b** (starting from 3 mmol of **1b**).

3i: δ_H (300 MHz, $CDCl_3$): 0.66 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), 1.07 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.26–1.63 (6H, m, $NCH_2(CH_2)_3$), 2.37–2.49 (5H, m, NCH_2CH_2 and $CH(CH_3)_2$), 3.21 (1H, d, J=10.1 Hz, C*H*C$H(CH_3)_2$), 3.64 (3H, s, NCH_3), 6.77 (1H, d, J=1.1 Hz, Im-H), 7.01 (1H, d, J=1.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 20.1, 20.3, 24.6, 26.4, 29.4, 32.8, 50.5, 66.9, 119.8, 126.8, 147.2. ν_{max} ($CHCl_3$, cm^{-1}): 1452, 1478, 1580, 2915. EI MS (*m*/*z*, %): 123 (98), 138 (87), 178 (100), 221 (M^+, 3). HRMS (EI): found M^+ 221.1891, $C_{13}H_{23}N_3$ requires M^+ 221.1892.

4i: δ_H (300 MHz, $CDCl_3$): 1.007 (3H, d, J=6.2 Hz, $CH(CH_3)_2$), 1.010 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), 1.42–1.59 (12H, m, $NCH_2(CH_2)_3$), 2.01–2.26 (3H, m, CH_2-C*H*$(CH_3)_2$), 2.40–2.62 (8H, m, NCH_2CH_2), 2.89 (3H, s, NCH_3), 4.00 (1H, d, J=3.7 Hz, Im-H), 4.23 (1H, d, J=3.5 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 22.4, 23.0, 24.5, 24.7, 26.0, 26.1, 26.6, 31.5, 36.5, 48.1, 49.1, 84.2, 85.8, 165.7. ν_{max} ($CHCl_3$, cm^{-1}): 1460, 1592, 2914. EI MS (*m*/*z*, %): 84 (91), 97 (100), 178 (90), 221 (25), 291 (20), 306 (M^+, 18). HRMS (EI): found M^+ 306.2779, $C_{18}H_{34}N_4$ requires M^+ 306.2783.

4.1.18. 2-(1-Benzylamino-2-methylpropyl)-1-methyl-1*H*-imidazole 3j. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:5), as a yellow viscous oil (176 mg, 36%) from benzylamine (10 mmol) and crude **2b** (starting from 2 mmol of **1b**).

δ_H (300 MHz, $CDCl_3$): 0.77 (3H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.05 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.95–2.11 (1H, m, C*H*$(CH_3)_2$), 2.22 (1H, br, N*H*CH_2), 3.41 (1H, d, J=7.9 Hz,

C*H*CH(CH_3)$_2$), 3.43 (1H, d, J=13.6 Hz, NCH_2), 3.48 (3H, s, NCH_3), 3.73 (1H, d, J=13.4 Hz, NCH_2), 6.76 (1H, d, J=1.1 Hz, Im-H), 7.01 (1H, d, J=0.9 Hz, Im-H), 7.18–7.32 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 19.5, 19.6, 32.5, 33.6, 51.5, 59.9, 120.3, 126.7, 127.2, 128.0, 128.2, 140.3, 149.7. ν_{max} ($CHCl_3$, cm^{-1}): 1460, 1485, 1599, 1657, 2950, 3300–3500. CI MS (*m*/*z*, %): 83 (12), 91 (62), 123 (22), 138 (50), 200 (100), 244 (M^++H, 52). HRMS (CI+): found MH^+ 244.1820, $C_{15}H_{21}N_3$+H requires MH^+ 244.1814.

4.1.19. (3*aR* *,7*aS* *)-3a,4,5,6,7,7a-Hexahydro-1,4,7-trimethyl-2-(2-methylpropyl)-1*H*-imidazo[4,5-*b*]pyrazine 4k. Obtained, after Al_2O_3 column chromatography (AcOEt/MeOH=10:1), as a yellow viscous oil (193 mg, 29%) from *N*,*N*′-dimethylethylenediamine (15 mmol) and crude **2b** (starting from 3 mmol of **1b**).

δ_H (300 MHz, $CDCl_3$): 1.015 (3H, d, J=6.4 Hz, CH(C*H*$_3$)$_2$), 1.019 (3H, d, J=6.6 Hz, CH(C*H*$_3$)$_2$), 1.98–2.10 (1H, m, C*H*(CH_3)$_2$), 2.20–2.30 (2H, m, C*H*$_2$CH(CH_3)$_2$), 2.53–2.84 (4H, m, (C*H*$_2$)$_2$), 2.50 (3H, s, NC*H*$_3$), 2.62 (3H, s, NC*H*$_3$), 2.89 (3H, s, NC*H*$_3$), 4.24 (1H, d, J=8.4 Hz, Im-H), 4.53 (1H, d, J=8.4 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 22.5, 22.6, 26.6, 32.2, 36.4, 42.0, 43.0, 44.6, 45.2, 77.4, 80.8, 168.1. ν_{max} ($CHCl_3$, cm^{-1}): 1450, 1598, 2919. EI MS (*m*/*z*, %): 85 (58), 114 (100), 142 (63), 185 (57), 198 (39), 224 (M^+, 2). HRMS (EI): found M^+ 224.1992, $C_{12}H_{24}N_4$ requires M^+ 224.2001.

4.1.20. *S*−2-Methyl-1-(1-methyl-1*H*-imidazol-2-yl)-propyl thiobenzoate 3l. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:2), as a yellow viscous oil (400 mg, 49%) from sodium benzenethioate (15 mmol), NaH (15 mmol) and crude **2b** (starting from 3 mmol of **1b**).

δ_H (300 MHz, $CDCl_3$): 1.00 (3H, d, J=6.6 Hz, CH(C*H*$_3$)$_2$), 1.16 (3H, d, J=7.0 Hz, CH(C*H*$_3$)$_2$), 2.42–2.58 (1H, m, C*H*(CH_3)$_2$), 3.71 (3H, s, NCH_3), 4.80 (1H, d, J=8.4 Hz, C*H*CH(CH_3)$_2$), 6.76 (1H, d, J=1.5 Hz, Im-H), 7.00 (1H, d, J=1.1 Hz, Im-H), 7.40–7.59 (3H, m, Ar-H), 7.95–7.99 (2H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 20.3, 20.8, 32.8, 33.1, 45.2, 120.3, 127.3, 127.9, 128.6, 133.5, 136.5, 147.5, 191.3. ν_{max} ($CHCl_3$, cm^{-1}): 1485, 1652, 1698, 2946. EI MS (*m*/*z*, %): 105 (55), 137 (100), 169 (99), 274 (M^+, 10). HRMS (EI): found M^+ 274.1152, $C_{15}H_{18}N_2OS$ requires M^+ 274.1140.

4.1.21. 1-Methyl-2-(1-dimethylaminoheptyl)-1*H*-imidazole 3m and (4*R* *,5*R* *)-2-heptyl-4,5-dihydro-1-methyl-4,5-bis(dimethylamino)-1*H*-imidazole 4m. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:1 to AcOEt only), as a yellow viscous oil [(**3m**; 69 mg, 31%), (**4m**; 124 mg, 46%)] from **2c** (1 mmol).

3m: δ_H (300 MHz, $CDCl_3$): 0.85 (3H, t, J=6.8 Hz, CH_2CH_3), 1.11–1.34 (8H, m, $CH_2(CH_2)_4CH_3$), 1.78–2.07 (2H, m, C*H*$_2$C$_5$H$_{11}$), 2.23 (6H, s, $N(CH_3)_2$), 3.56 (1H, dd, J=4.6, 10.1 Hz, C*H*C$_6$H$_{13}$), 3.67 (3H, s, NCH_3), 6.80 (1H, d, J=1.1 Hz, Im-H), 6.96 (1H, d, J=1.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 14.0, 22.5, 27.0, 28.1, 29.3, 31.7, 32.7, 41.6, 61.5, 120.8, 126.7, 147.5. ν_{max} ($CHCl_3$, cm^{-1}): 1455, 1480, 2763, 2909. EI MS (*m*/*z*, %): 96 (32), 109 (100), 138 (43), 180 (68), 223 (M^+, 1). HRMS (EI): found M^+ 223.2034, $C_{13}H_{25}N_3$ requires M^+ 223.2048.

4m: δ_H (300 MHz, $CDCl_3$): 0.88 (3H, t, J=6.8 Hz, CH_2CH_3), 1.28–1.41 (8H, m, $CH_2(CH_2)_4CH_3$), 1.59–1.69 (2H, m, C*H*$_2$C$_5$H$_{11}$), 2.21 (6H, s, $N(CH_3)_2$), 2.19–2.30 (2H, m, C*H*$_2$C$_6$H$_{13}$), 2.27 (6H, s, $N(CH_3)_2$), 2.90 (3H, s, NCH_3), 3.96 (1H, d, J=3.5 Hz, Im-H), 4.20 (1H, d, J=3.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 13.9, 22.4, 26.9, 27.9, 28.9, 29.5, 30.8, 31.6, 38.3, 39.9, 82.6, 85.4, 166.6. ν_{max} ($CHCl_3$, cm^{-1}): 1449, 1594, 2773, 2907. EI MS (*m*/*z*, %): 124 (33), 139 (100), 152 (44), 223 (45), 268 (M^+, 7). HRMS (EI): found M^+ 268.2620, $C_{15}H_{32}N_4$ requires M^+ 268.2627.

4.1.22. 1-Methyl-2-[1-(1-pyrrolidinyl)heptyl]-1*H*-imidazole 3n and (4*R* *,5*R* *)-2-heptyl-4,5-dihydro-1-methyl-4,5-bis(1-pyrrolidinyl)-1*H*-imidazole 4n. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:2 to AcOEt only), as a yellow viscous oil [(**3n**; 106 mg, 43%), (**4n**; 130 mg, 41%)] from pyrrolidine (5 mmol) and **2c** (1 mmol).

3n: δ_H (300 MHz, $CDCl_3$): 0.84 (3H, t, J=6.8 Hz, CH_2CH_3), 0.98–1.30 (8H, m, $CH_2(CH_2)_4CH_3$), 1.65–1.77 (4H, m, $NCH_2(CH_2)_2$), 1.84–2.00 (2H, m, C*H*$_2$C$_5$H$_{11}$), 2.25–2.38 (2H, m, NC*H*$_2$CH$_2$), 2.60–2.68 (2H, m, NC*H*$_2$CH$_2$), 3.62 (1H, dd, J=5.7, 9.4 Hz, C*H*C$_6$H$_{13}$), 3.72 (3H, s, NCH_3), 6.77 (1H, d, J=1.1 Hz, Im-H), 6.93 (1H, d, J=1.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 13.9, 22.4, 23.1, 26.4, 29.2, 31.6, 32.5, 32.8, 51.0, 61.5, 120.7, 126.7, 148.2. ν_{max} ($CHCl_3$, cm^{-1}): 1457, 1493, 2780, 2909. EI MS (*m*/*z*, %): 96 (24), 109 (100), 180 (65), 249 (M^+, 1). HRMS (EI): found M^+ 249.2207, $C_{15}H_{27}N_3$ requires M^+ 249.2205.

4n: δ_H (300 MHz, $CDCl_3$): 0.88 (3H, t, J=6.8 Hz, CH_2CH_3), 1.23–1.40 (8H, m, $CH_2(CH_2)_4CH_3$), 1.56–1.82 (10H, m, C*H*$_2$C$_5$H$_{11}$, and NCH_2CH_2), 2.26 (2H, t, J=7.9 Hz, C*H*$_2$C$_6$H$_{13}$), 2.60–2.77 (8H, m, NC*H*$_2$CH$_2$), 2.91 (3H, s, NCH_3), 4.26 (1H, d, J=3.1 Hz, Im-H), 4.32 (1H, d, J=3.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 13.9, 22.4, 23.2, 23.7, 26.8, 28.0, 28.9, 29.5, 31.4, 31.6, 46.4, 48.5, 82.2, 82.6, 166.6. ν_{max} ($CHCl_3$, cm^{-1}): 1476, 1593, 1666, 2906. EI MS (*m*/*z*, %): 71 (54), 165 (96), 178 (37), 249 (100), 320 (M^+, 13). HRMS (EI): found M^+ 320.2924, $C_{19}H_{36}N_4$ requires M^+ 320.2940.

4.1.23. 1-Benzyl-2-(1-dimethylamino-2,2-dimethylpropyl)-1*H*-imidazole 3p and (4*R* *,5*R* *)-1-benzyl-4,5-dihydro-4,5-bis(dimethylamino)-2-(2,2,-dimethylpropyl)-1*H*-imidazole 4p. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:3 to AcOEt only), as a yellow viscous oil (**3p**; 32 mg, 12%) and a solid (**4p**; 253 mg, 80%) from **2d** (1 mmol).

3p: δ_H (300 MHz, $CDCl_3$): 0.97 (9H, s, C(CH_3)$_3$), 2.30 (6H, s, $N(CH_3)_2$), 3.37 (1H, s, C*H*C(CH_3)$_3$), 5.12 and 5.18 (1H each, each d, J=15.8 Hz, NCH_2), 6.85 (1H, d, J=1.3 Hz, Im-H), 7.11 (1H, d, J=1.1 Hz, Im-H), 7.12–7.37 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 27.8, 37.2, 45.0, 50.0, 67.2, 119.5, 127.0, 127.2, 128.0, 128.8, 136.7, 146.0. ν_{max} ($CHCl_3$, cm^{-1}): 1450, 1471, 2928. EI MS (*m*/*z*, %): 91 (12), 123 (3), 173 (2), 214 (100), 257 (3), 271 (M^+, 1).

HRMS (EI): found M^+ 271.2041, $C_{17}H_{25}N_3$ requires M^+ 271.2048.

4p: δ_H (300 MHz, $CDCl_3$): 1.11 (9H, s, $C(CH_3)_3$), 2.18 (6H, s, $N(CH_3)_2$), 2.21 (6H, s, $N(CH_3)_2$), 2.37 (2H, s, $CH_2C(CH_3)_3$), 3.91 (1H, d, J=4.0 Hz, Im-H), 4.27 (1H, d, J=15.8 Hz, NCH_2), 4.33 (1H, d, J=4.4 Hz, Im-H), 4.57 (1H, d, J=15.4 Hz, NCH_2), 7.21–7.35 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 30.2, 31.7, 38.4, 40.3, 40.4, 47.3, 81.1, 82.2, 127.4, 127.8, 128.5, 137.3, 164.1. ν_{max} ($CHCl_3$, cm^{-1}): 1587, 2923, 3132. EI MS (*m*/*z*, %): 91 (17), 124 (53), 214 (100), 225 (69), 271 (96), 316 (M^+, 2). HRMS (EI): found M^+ 316.2613, $C_{19}H_{32}N_4$ requires M^+ 316.2627.

4.1.24. 1-Benzyl-2-[2,2-dimethyl-1-(1-pyrrolidinyl)-propyl]-1*H*-imidazole 3q and (4*R,5*R**)-1-benzyl-4,5-dihydro-2-(2,2-dimethylpropyl)-4,5-bis(1-pyrrolidinyl)-1*H*-imidazole 4q.** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:3 to AcOEt only), as a yellow viscous oil (**3q**; 27 mg, 18%) and a solid (**4q**; 132 mg, 72%) from pyrrolidine (2.5 mmol) and **2d** (0.5 mmol).

3q: δ_H (300 MHz, $CDCl_3$): 0.99 (9H, s, $C(CH_3)_3$), 1.54–1.67 (4H, m, $NCH_2(CH_2)_2$), 2.30–2.85 (4H, m, NCH_2CH_2), 3.65 (1H, s, $CHC(CH_3)_3$), 5.14 (2H, s, NCH_2), 6.82 (1H, d, J=1.3 Hz, Im-H), 7.09 (1H, d, J=1.3 Hz, Im-H), 7.11–7.37 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 23.6, 28.1, 37.0, 50.0, 52.1, 64.8, 119.3, 127.2, 127.3, 128.0, 128.8, 136.5, 146.7. ν_{max} ($CHCl_3$, cm^{-1}): 1451, 1473, 2937. EI MS (*m*/*z*, %): 91 (13), 213 (12), 240 (100), 297 (M^+, 0.2). HRMS (EI): found M^+ 297.2224, $C_{19}H_{27}N_3$ requires M^+ 297.2205.

4q: δ_H (300 MHz, $CDCl_3$): 1.09 (9H, s, $C(CH_3)_3$), 1.67–1.76 (8H, m, $NCH_2(CH_2)_2$), 2.34 (2H, s, $CH_2(CH_3)_3$), 2.57–2.67 (8H, m, NCH_2CH_2), 4.28 (1H, d, J=4.0 Hz, Im-H), 4.29 (1H, d, J=15.8 Hz, NCH_2), 4.53–4.59 (2H, m, Im-H and NCH_2), 7.22–7.34 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 23.5, 24.0, 30.2, 31.7, 40.4, 46.5, 47.7, 47.8, 77.9, 80.9, 127.2, 127.6, 128.4, 137.8, 164.0. ν_{max} ($CHCl_3$, cm^{-1}): 1457, 1586, 2933. EI MS (*m*/*z*, %): 70 (51), 91 (93), 150 (42), 240 (100), 277 (86), 297 (36), 368 (M^+, 1). HRMS (EI): found M^+ 368.2952, $C_{23}H_{36}N_4$ requires M^+ 368.2940.

4.1.25. 1-Benzyl-2-[1-(1-methylethoxy)-2,2-dimethyl-propyl]-1H-imidazole 3r. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:2), as colorless needles (48 mg, 34%) from 2-propanol (5 mmol), Et_3N (3 mmol) and **2d** (0.5 mmol). Mp 47–50 °C.

δ_H (300 MHz, $CDCl_3$): 0.92 (3H, d, J=5.9 Hz, $CH(CH_3)_2$), 0.97 (9H, s, $C(CH_3)_3$), 1.02 (3H, d, J=6.2 Hz, $CH(CH_3)_2$), 3.42 (1H, hept., J=6.1 Hz, $CH(CH_3)_2$), 4.39 (1H, s, $CHC(CH_3)_3$), 5.21 and 5.50 (1H each, each d, J=15.8 Hz, NCH_2), 6.72 (1H, d, J=1.5 Hz, Im-H), 7.01 (1H, d, J=1.1 Hz, Im-H), 7.09–7.12 (2H, m, Ar-H), 7.27–7.36 (3H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.0, 22.8, 26.7, 36.7, 50.4, 70.7, 82.0, 120.5, 127.0, 127.5, 127.7, 128.7, 137.3, 147.2. ν_{max} ($CHCl_3$, cm^{-1}): 1475, 2931. EI MS (*m*/*z*, %): 91 (43), 187 (100), 229 (79), 286 (M^+, 4). HRMS (EI): found M^+ 286.2037, $C_{18}H_{26}N_2O$ requires M^+ 286.2045.

4.1.26. 1-Benzyl-2-(2,2-dimethyl-1-phenoxypropyl)-1*H*-imidazole 3s. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:3), as a colorless powder (82 mg, 51%) from phenol (3 mmol), Et_3N (2.5 mmol) and **2d** (0.5 mmol). Mp 84–87 °C.

δ_H (300 MHz, $CDCl_3$): 1.14 (9H, s, $C(CH_3)_3$), 5.06 and 5.37 (1H each, each d, J=15.4 Hz, NCH_2), 5.19 (1H, s, $CHC(CH_3)_3$), 6.58 (1H, d, J=1.1 Hz, Im-H), 6.74–6.91 (5H, m, Ar-H), 7.02 (1H, d, J=1.5 Hz, Im-H), 7.11–7.18 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 26.7, 37.1, 50.6, 83.7, 115.5, 120.6, 121.1, 127.5, 127.6, 127.9, 128.5, 129.4, 136.4, 144.9, 158.2. ν_{max} ($CHCl_3$, cm^{-1}): 1489, 1584, 1595, 2936. EI MS (*m*/*z*, %): 91 (15), 169 (4), 227 (100), 263 (12), 320 (M^+, 1). HRMS (EI): found M^+ 320.1886, $C_{21}H_{24}N_2O$ requires M^+ 320.1889.

4.1.27. 2-(2,2-Dimethyl-1-dimethylaminopropyl)-1*H*-imidazole 3t. Obtained, after recrystallization of the crude extracts from AcOEt, as colorless prisms (150 mg, 83%) from **2e** (starting from 1 mmol of **1e**). Mp 134–136 °C.

δ_H (300 MHz, DMSO-d_6): 0.97 (9H, s, $C(CH_3)_3$), 2.15 (6H, s, $N(CH_3)_2$), 3.24 (1H, s, $CHC(CH_3)_3$), 6.87 (1H, br, Im-H), 6.99 (1H, br, Im-H). δ_C (75 MHz, DMSO-d_6): 27.6, 35.9, 44.8, 70.2, 114.5, 127.2, 144.7. ν_{max} (KBr, cm^{-1}): 1441, 2807, 2931, 3097. EI MS (*m*/*z*, %): 83 (21), 95 (8), 108 (6), 124 (100), 181 (M^+, 3). HRMS (EI): found M^+ 181.1589, $C_{10}H_{19}N_3$ requires M^+ 181.1579. Anal. calcd for $C_{10}H_{19}N_3$: C, 66.26; H, 10.56; N, 23.18; found: C, 66.09; H, 10.57; N, 23.14.

4.2. Synthesis of 5-amino-1-methylimidazoles 7

A toluene (1 mL) solution of **4** (0.5 mmol) was heated at 120 °C with stirring under N_2 until no starting material (**4**) remained on TLC (5–12 h). The solution was cooled to rt, and the solvent was evaporated to give an oily residue, which was purified by Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:2 to AcOEt only) to obtain pure **7** as a yellow viscous oil.

4.2.1. 1-Methyl-5-dimethylamino-2-(2,2-dimethyl-propyl)-1*H*-imidazole 7a. Yield, 88 mg (90%). δ_H (300 MHz, $CDCl_3$): 1.00 (9H, s, $C(CH_3)_3$), 2.51 (2H, s, $CH_2C(CH_3)_3$), 2.64 (6H, s, $N(CH_3)_2$), 3.40 (3H, s, NCH_3), 6.50 (1H, s, Im-H). δ_C (75 MHz, $CDCl_3$): 29.5, 29.6, 32.7, 40.4, 44.8, 112.8, 143.0, 143.8. ν_{max} ($CHCl_3$, cm^{-1}): 1465, 1491, 1567, 2926. EI MS (*m*/*z*, %): 70 (9), 138 (100), 180 (4), 195 (M^+, 14). HRMS (EI): found M^+ 195.1720, $C_{11}H_{21}N_3$ requires M^+ 195.1735.

4.2.2. 1-Methyl-2-(2,2-dimethylpropyl)-5-(1-pyrrolidinyl)-1*H*-imidazole 7b. Yield, 92 mg (83%). δ_H (300 MHz, $CDCl_3$): 0.99 (9H, s, $C(CH_3)_3$), 1.90–1.95 (4H, m, $NCH_2(CH_2)_2$), 2.52 (2H, s, $CH_2C(CH_3)_3$), 3.00–3.05 (4H, m, NCH_2CH_2), 3.41 (3H, s, NCH_3), 6.46 (1H, s, Im-H). δ_C (75 MHz, $CDCl_3$): 24.5, 29.6, 30.3, 32.8, 40.4, 52.8, 111.6, 141.8, 142.9. ν_{max} ($CHCl_3$, cm^{-1}): 1464, 1490, 1566, 2934. EI MS (*m*/*z*, %): 96 (3), 122 (6), 164 (100), 206 (4), 221 (M^+, 14). HRMS (EI): found M^+ 221.1898, $C_{13}H_{23}N_3$ requires M^+ 221.1892.

4.2.3. 1-Methyl-5-dimethylamino-2-(2-methylpropyl)-1*H*-imidazole 7c. Yield, 60 mg (66%). δ_H (300 MHz,

$CDCl_3$): 0.97 (6H, d, J=6.6 Hz, $CH(CH_3)_2$), 2.01–2.17 (1H, m, $CH(CH_3)_2$), 2.48 (2H, d, J=7.3 Hz, $CH_2CH(CH_3)_2$), 2.64 (6H, s, $N(CH_3)_2$), 3.38 (3H, s, NCH_3), 6.47 (1H, s, Im-H). δ_C (75 MHz, $CDCl_3$): 22.5, 27.7, 28.9, 36.5, 44.9, 112.7, 143.8, 144.1. ν_{max} ($CHCl_3$, cm^{-1}): 1461, 1497, 1568, 2933. EI MS (*m*/*z*, %): 70 (12), 124 (5), 138 (100), 166 (6), 181 (M^+, 26). HRMS (EI): found M^+ 181.1585, $C_{10}H_{19}N_3$ requires M^+ 181.1579.

4.2.4. 1-Methyl-2-(2-methylpropyl)-5-(1-pyrrolidinyl)-1*H*-imidazole 7d. Yield, 83 mg (80%). δ_H (300 MHz, $CDCl_3$): 0.97 (6H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.87–1.96 (4H, m, $NCH_2(CH_2)_2$), 2.00–2.18 (1H, m, $CH(CH_3)_2$), 2.48 (2H, d, J=7.2 Hz, $CH_2CH(CH_3)_2$), 3.00–3.04 (4H, m, NCH_2CH_2), 3.40 (3H, s, NCH_3), 6.42 (1H, s, Im-H). δ_C (75 MHz, $CDCl_3$): 22.5, 24.4, 27.8, 29.4, 36.5, 52.8, 111.6, 141.7, 143.8. ν_{max} ($CHCl_3$, cm^{-1}): 1459, 1496, 1567, 2938. EI MS (*m*/*z*, %): 96 (4), 122 (8), 164 (100), 207 (M^+, 19). HRMS (EI): found M^+ 207.1750, $C_{12}H_{21}N_3$ requires M^+ 207.1735.

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