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Isoprene-catalysed lithiation: deprotection and functionalisation of imidazole derivatives

Rosario Torregrosa, Isidro M. Pastor and Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

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Dedicated in the memory of Professor G. Ourisson

Abstract—The isoprene-catalysed lithiation of different 1-substituted imidazoles (**1**) (such as trityl, allyl, benzyl, vinyl, *N*,*N*-dimethylsulfamoyl, *para*-toluenesulfonyl, *tert*-butoxycarbonyl, acetyl, trimethylsilyl, *tert*-butyldimethylsilyl derivatives) leads to the cleavage of the protecting group producing 1*H*-imidazole. The use of 1-(diethoxymethyl)imidazole (**3**) in the same lithiation reaction allows the preparation of the corresponding 2-lithio intermediate, which by reacting with different electrophiles leads to 2-functionalised imidazoles **4**.

1. Introduction

The synthesis of products containing heterocycles is a broad field of interest, especially in the case of azoles, which are amply present in compounds with pharmacological and biological properties.[1] Ring-closure reactions of acyclic precursors and substituent modifications of heterocyclic compounds are the two main routes for the general preparation of heterocyclic derivatives. Metallated imidazole intermediates (mainly prepared from the corresponding lithium precursors) have been widely used in the preparation of heterocyclic derivatives,[2] these compounds have broad application in synthetic organic chemistry.[3,4] Alkyllithium reagents and lithium amides have been reported as reagents for these lithiation processes (hydrogen–lithium and halogen–lithium exchanges), and reaction conditions usually involve low temperature in an ethereal solvent.[2,5,6]

Lithium metal is commonly used as a lithiation agent, albeit it needs activation due to its low reactivity under some reaction conditions. This activation can be done by compounds acting as electron carriers, so the use of an arene in substoichiometric amount has shown to be a very efficient protocol for this procedure.[7] By means of this procedure different functionalised organolithium reagents have been prepared starting from a variety of substrates such as halogenated[4,8] or non-halogenated[9] compounds, as well as heterocyclic precursors.[10] The arene-catalysed lithiation methodology has also proved to be useful for the removal of some commonly employed protective groups: allylic and benzylic alcohols and *N*-substituted-sulfonamides and -carboxamides were cleaved under very mild conditions[11] and, more recently, deprotection of trityl ethers,[12] tritylamines,[13] silyl,[14] allyloxycarbonyl,[15] benzyloxycarbonyl,[15] pivaloyl[16] and benzoyl[16] alcohols, amines and thiols has also been reported.

On the other hand, lithium metal has also been described to be useful in the preparation of lithium imidazole intermediates, so we have recently developed a new protocol to prepare 2-lithioimidazole using lithium powder in the presence of a substoichiometric amount of isoprene.[17] By reacting this organolithium with carbonyl and imine electrophiles the corresponding 2-(hydroxyalkyl)- and 2-(aminoalkyl)-1-methylimidazole derivatives were obtained. However, this methodology did not allow the direct lithiation of imidazole because after the N-deprotonation a second lithiation did not occur. In this article, we report the application of this lithiation methodology to both the removal of the protective group in several *N*-protected imidazoles and for the preparation of 2-functionalised-1*H*-imidazoles.

2. Results and discussion

During the course of our studies on the preparation of imidazole derivatives using an isoprene-catalysed lithiation process we decided to examine different *N*-protected imidazoles with this protocol. The trityl group has been used to protect simple imidazoles and although it is usually cleaved under acidic conditions or by hydrogenation,[18] we observed that lithiation conditions can be also used for the same detritylation. Thus, when *N*-tritylimidazole (**1a**) was treated with an excess of lithium powder in the presence of 1 equiv of isoprene (100 mol %) at room temperature imidazole (**2**) was

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* Corresponding author. Fax: +34 965 903549; e-mail: yus@ua.es

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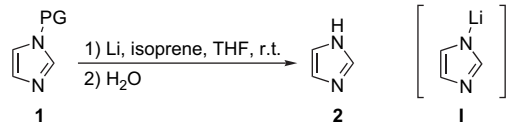
Table 1. Deprotection of *N*-protected-imidazoles via isoprene-catalysed lithiation process[a]



1 **2** **I**

Entry	Substrate		Isoprene (%)	Yield (%)[b]
	No.	PG		
1	**1a**	Tr	0	45
2	**1a**	Tr	50	74
3	**1a**	Tr	100	95
4	**1a**	Tr	5 (DTBB 5 mol %)	47 (58)[c]
5	**1b**	Allyl	0	54
6	**1b**	Allyl	50	67
7	**1b**	Allyl	100	85
8	**1c**	Bn	0	55
9	**1c**	Bn	100	74
10	**1d**	Vinyl	0	24
11	**1d**	Vinyl	100	43
12	**1e**	$-SO_2NMe_2$	0	<5
13	**1e**	$-SO_2NMe_2$	100	49
14	**1f**	Ts	0	49
15	**1f**	Ts	100	88
16	**1g**	Boc	0	22
17	**1g**	Boc	100	90
18	**1h**	Acetyl	0	74
19	**1h**	Acetyl	100	99
20	**1i**	$-SiMe_3$	0	88
21	**1i**	$-SiMe_3$	100	94
22	**1j**	$-SiBu^tMe_2$	0	82
23	**1j**	$-SiBu^tMe_2$	100	85

[a] Reaction carried out with protected imidazole, lithium (3 mmol/mmol of substrate), THF (10 mL), 23 °C.
[b] Isolated yield of pure product **2**. Purification was done by recrystallisation.
[c] Reaction carried out with 1-tritylimidazole (2 mmol), lithium (6 mmol), DTBB (5 mol %), THF (20 mL), 23 °C.

isolated with 95% yield (Table 1, entry 3), the intermediate **I** probably being involved in the process. Further studies showed that in the absence of isoprene, lithium partially caused the reductive cleavage of the trityl group producing imidazole in 45% yield after 1 h reaction (Table 1, entry 1), and using half an equivalent of isoprene the yield was risen up to 74% (Table 1, entry 2). In all cases, the corresponding triphenylmethane was detected in the reaction mixture (GC and ^1H NMR). Naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB) have been reported to catalyse a lithiation process to efficiently detritylate *N*-tritylamines,[13] thus the use of 5 mol % of DTBB together with an excess of lithium gave imidazole with a slightly better yield (58%, Table 1, entry 4 and footnote c) compared with the reaction without catalyst (45%, Table 1, entry 1) or the use of 5 mol % of isoprene (47%, Table 1, entry 4).

In general, the allyl moiety is usually cleaved in *N*-allylamines, like the corresponding allyl ethers, by treatment with transition metal reagents.[19] Regarding *N*-allylated imidazole (**1b**), it has only been reported to undergo deallylation by treatment with diisobutylaluminium hydride in the presence of a catalytic amount of $Ni(dppp)Cl_2$ producing imidazole with 81% yield.[20] Under our reductive conditions, lithium powder was able to deprotect *N*-allylimidazole (**1b**) at room temperature with 54% yield (Table 1, entry 5), albeit the use of isoprene improved the process up to 85% yield when using 1 equiv of the diene (Table 1, entries 6 and 7).

It is also known that *N*-benzyl protective groups may be removed by reductive conditions, the major drawback when using this protective group being the competitive α-metallation.[6] The 1-benzyl-2-imidazolyl anion appears to be thermodynamically preferred to the $N-C_\alpha$ anion but it is not clear which of the two possible anions is kinetically favoured.[21] The reaction of 1-benzylimidazole (**1c**) with lithium in the presence of 1 equiv of isoprene at room temperature gave after 1 h the corresponding debenzylated imidazole with 74% yield (Table 1, entry 9). The only use of lithium (without catalyst) caused around half of the cleavage of the benzyl group (Table 1, entry 8), as previously commented for trityl and allyl groups.

Our study continued with 1-vinylimidazole (**1d**). The vinyl group has been used to protect imidazole derivatives and it is usually cleaved by ozonolysis or by using potassium permanganate.[22] The vinyl group showed to be less susceptible to the reductive process, so when the compound **1d** was subjected to the isoprene-catalysed lithiation protocol only 43% of the imidazole was isolated after the reaction (Table 1, entry 11). Anyway, the isoprene improved the cleavage process, since the absence of isoprene yielded only 24% of product **2** (Table 1, entry 10).

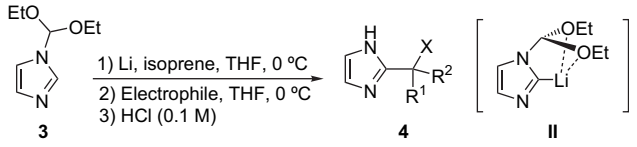
Next we decided to investigate the deprotection of other groups at the nitrogen, such as *N*-sulfonyl, *N*-carbonyl and *N*-alkyloxycarbonyl derivatives. The *N*,*N*-dimethylsulfamoyl group has been commonly used during the synthesis of imidazole-containing compounds with potential biological and pharmaceutical activity and the removal of the sulfamoyl group requires relatively vigorous acidic conditions (generally, refluxing 30% HBr or refluxing 2 N HCl).[23,24] The sulfonamide **1e** (prepared in 93% yield from imidazole and *N*,*N*-dimethylchlorosulfonamide in the presence of triethylamine) showed higher stability under reductive conditions, thus almost all the starting material was recovered when compound **1e** was treated with lithium (less than 5% deprotection, Table 1, entry 12). In the presence of 1 equiv of isoprene 49% of the imidazole was isolated (Table 1, entry 13). In contrast, the deprotection of *N*-(*para*-toluenesulfonyl)-imidazole[25] (**1f**) under the same reaction conditions proceeded smoothly to give up to 88% yield (Table 1, entries 14 and 15). Similar results were obtained when 1-(*tert*-butoxycarbonyl)imidazole (**1g**) was subjected to the commented protocol, although higher influence of the amount of isoprene was observed (Table 1, entries 16 and 17).[26] Finally, *N*-acetylimidazole (**1h**) proved to be very labile under the assayed reductive conditions, even in the absence of isoprene (Table 1, entries 18 and 19).

During the studies of stabilities of different nitrogen protective groups in the imidazole, we tested trialkylsilyl derivatives, such as 1-(trimethylsilyl)imidazole (**1i**) and 1-(*tert*-butyldimethylsilyl)imidazole (**1j**) and, as expected, the nitrogen–silicon bond was cleaved in high yield under lithiation with (94 and 85%, respectively, using 100% isoprene, Table 1, entries 21 and 23) or without (88 and 82%, respectively, Table 1, entries 20 and 22) isoprene catalysis.

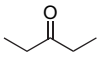
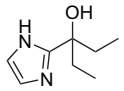
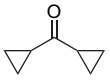
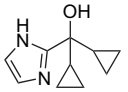
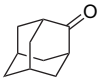
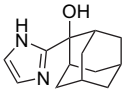
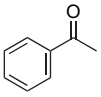
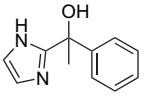
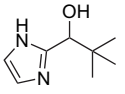
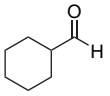
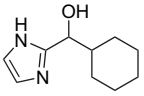
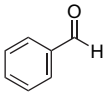
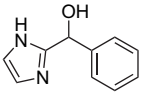
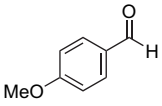
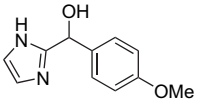
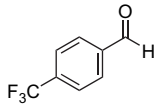
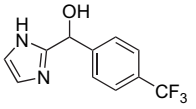
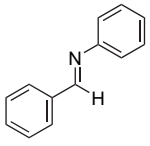
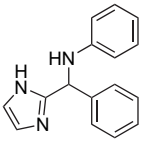
On the other hand, 1-(diethoxymethyl)imidazole (**3**) showed to be very stable when it was treated with lithium powder and isoprene, even at room temperature (<10% imidazole

2 detected by ^{1}H NMR). Thus, our next consideration was to try our lithiation methodology with compound **3** in order to obtain, after deprotection,[27–29] 2-functionalised-1*H*-imidazole derivatives, which are not available by direct lithiation–S_E reaction from imidazole itself (see above). Compound **3** was treated first with an excess of lithium powder in the presence of isoprene (100 mol %) and then with different electrophiles giving after quenching in acidic aqueous medium the corresponding 2-substituted-1*H*-imidazoles **4** with moderate to high yields (Table 2) via the chelated intermediate **II**, which is stabilised by CIPE (Complex Induced Proximity Effect).[30] The use of half an equivalent of isoprene gave lower yield of the final product, thus 3-(1*H*-2-imidazolyl)-3-pentanol (**4a**) was obtained with 63% yield instead of 75% (Table 2, entry 1, footnote c). Ketones gave in general better results than aldehydes or an aldimine (Table 2, compare entries 1–4 with 5–10). Aromatic carbonylic compounds reacted less effectively than the aliphatic ones and in the case of substituted benzaldehyde no improvement in the yield was observed using either electron-donating or electron-withdrawing substituents (Table 2, entries 8 and 9).

Table 2. Preparation of 2-functionalised-1*H*-imidazole derivatives[a]



3 4 II

Entry	Electrophile	Product		
		No.	Structure	Yield (%)[b]
1		**4a**		75 (63)[c]
2		**4b**		93
3		**4c**		91
4		**4d**		55
5		**4e**		92
6		**4f**		51
7		**4g**		59
8		**4h**		57
9		**4i**		58
10		**4j**		48

[a] Reaction carried out with 1-(diethoxymethyl)imidazole (**3**, 3 mmol), lithium (9 mmol), isoprene (3 mmol), THF (7 mL), 0 °C, and then added the electrophile (3.6 mmol).
[b] Isolated yield of pure product. Purification was done by recrystallisation.
[c] Reaction carried out using only 1.5 mmol (50 mol %) of isoprene.

3. Conclusions

In conclusion, we have reported here an efficient procedure to remove several protective groups from the imidazolic nitrogen under mild reaction conditions. The lithium/isoprene methodology is applicable to successfully cleave sulfonyl, carbonyl, alkoxycarbonyl, trialkylsilyl and carbon substituents (such as vinyl, trityl, benzyl and allyl). The treatment of 1-(diethoxymethyl)imidazole with a slight excess of lithium metal in the presence of isoprene gave no scission of this group and produced the corresponding organolithium. This intermediate was reacted with different electrophiles (carbonyl compounds or imines)[31] producing, after acidic hydrolysis, the corresponding 2-(hydroxyalkyl)- or 2-(*N*-phenylamino)benzyl)-1*H*-imidazole derivatives with moderate to excellent yields.

4. Experimental

4.1. General

All lithiation reactions were carried out under argon atmosphere in oven-dried glassware. All commercially available reagents (Acros, Aldrich, Fluka) were used without further purification, except in the case of liquid electrophiles, which were used freshly distilled. Commercially available anhydrous THF (99.9%, water content ≤0.006%, Fluka) was used as the solvent in all the lithiation reactions. Melting points were obtained with an MPA100 Optimelt SRS apparatus. IR spectra were measured with a Nicolet Impact 400 D-FT Spectrometer. NMR spectra were recorded on a Bruker Avance 300 and Bruker Avance 400 (300 and 400 MHz for ^{1}H NMR, and 75 and 100 MHz for ^{13}C NMR) using, except otherwise stated, $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in δ (ppm) and coupling constants (J) in Hz. Mass spectra (EI) were obtained at 70 eV on an Agilent 5973 spectrometer, fragment ions in m/z with relative intensities (%) in parenthesis and High Resolution Mass Spectra (HRMS) analyses were carried out on a Finnigan MAT95S spectrometer, when indicated the samples were inserted in the modality of Direct Insertion Probe (DIP). The purity of volatile compounds and the chromatographic analyses (GLC) were determined with an Agilent 6890N instrument equipped with a flame ionisation detector and a 30 m capillary column (0.25 mm diameter, 0.25 μm film thickness), using nitrogen (2 ml/min) as carrier gas, $T_{injector}$=275 °C, T_{column}=60 °C (3 min) and 60–270 °C (15 °C/min); retention times (t_R) are given in minutes under these conditions. Thin layer chromatography was carried out

on TLC plastic sheets with silica gel 60 F_{254} (Merck). Lithium powder was commercially available (MEDALCHEMY S.L.).

4.2. General procedure for the deprotection of 1-protected imidazoles

A solution of the corresponding 1-protected imidazole (**1**, 2 mmol) in THF (2–15 mL depending on the substrate) was added to a suspension of lithium powder (42 mg, 6 mmol) and isoprene (0.202 mL, 2 mmol) in THF (2 mL) at room temperature for 1 h. The reaction mixture was quenched with water (1 mL), and then ethyl acetate was also added (30 mL). The mixture was filtered and the precipitate washed with ethyl acetate (10 mL). The filtrate and the washings were combined and the solvent was evaporated under vacuum (15 Torr). The imidazole (**2**) was purified by recrystallisation (mixtures of ethyl acetate and *n*-pentane). In all cases, compound **2** was characterised by comparison of its ^{1}H NMR and ^{13}C NMR with those of the literature.[32]

4.3. *N*,*N*-Dimethyl-1*H*-imidazole-1-sulfonamide (1e)[24]

A solution of dimethylchlorosulfonamide (1.19 mL, 11 mmol), imidazole (0.69 g, 10 mmol) and triethylamine (1.7 mL, 12 mmol) in toluene (16 mL) was stirred at room temperature for 16 h. The resulting mixture was filtered and the precipitate washed with toluene (10 mL). The filtrate and the washings were combined and the solvent was evaporated under vacuum (15 Torr). The product was obtained by distillation of the impurities (ca. 60 °C, 0.1 Torr). Obtained 1.61 g (93% yield); white solid (formed on standing); t_R 10.44; mp 41–43 °C; δ_H (400 MHz, $CDCl_3$): 2.86 (6H, s, 2×CH_3), 7.15, 7.31 (1H and 1H, 2s, NCHCHN), 7.93 (1H, s, NCHN); δ_C (100 MHz, $CDCl_3$): 37.6 (2C, CH_3), 117.3, 130.0 (2C, NCHCHN), 136.2 (NCHN); *m*/*z* 177 (M^++2, 2%), 176 (3), 175 (31), 108 (100), 69 (20).

4.4. 1-(Diethoxymethyl)-1*H*-imidazole (3)[27–29]

A solution of imidazole (6.87 g, 0.1 mol) and *para*-toluenesulfonic acid (0.5 g) in triethyl orthoformate (67 mL, 0.4 mol) was heated at 130 °C until no more ethanol was distilled (ca. 4 h). The excess of orthoformate was distilled under vacuum (75–79 °C, 15 Torr) and Na_2CO_3 (0.5 g) was added to the reaction mixture. The product was obtained pure by distillation (85 °C, 0.1 Torr). Obtained 14.50 g (85% yield). Colourless oil; t_R 9.99; δ_H (300 MHz, $CDCl_3$): 1.25 (6H, t, *J*=7.0 Hz, 2×CH_3), 3.59 (4H, q, *J*=7.0 Hz, 2×CH_2), 6.06 (1H, s, C*H*($OEt)_2$), 7.07, 7.10 (2H, 2s, CHCH), 7.73 (1H, s, NCHN); δ_C (75 MHz, $CDCl_3$): 14.6 (2C, 2×CH_3), 60.9 (2C, 2×CH_2), 101.3 (*C*H($OEt)_2$), 116.1, 129.3 (CHCH), 135.0 (NCN); *m*/*z* 170 (M^+, 0.75%), 125 (20), 103 (100), 97 (24), 75 (41), 69 (15), 68 (22).

4.5. General procedure for the preparation of 2-functionalised-1*H*-imidazoles (4)

A solution of 1-(diethoxymethyl)-1*H*-imidazole (**3**, 0.51 g, 3 mmol) in THF (2 mL) was added to a suspension of lithium powder (63 mg, 9 mmol) and isoprene (0.303 mL, 3 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 90 min and then the corresponding electrophile (3.6 mmol) was added, continuing the stirring for 45 min at the same temperature. The resulting solution was filtered over HCl (0.1 M, 15 mL) at 0 °C, and the organic layer was extracted with HCl (0.1 M, 4×15 mL). The resulting aqueous phase was neutralised with $NaHCO_3$, then extracted with ethyl acetate (4×20 mL) and finally dried over anhydrous magnesium sulfate. After removing the solvent under reduced pressure (15 Torr), the corresponding products **4** were obtained by recrystallisation.

4.5.1. 3-(1*H*-2-Imidazolyl)-3-pentanol (4a). Obtained 0.34 g (75% yield) [recrystallisation (ethyl acetate/diethyl ether)]; white solid; mp 140–142 °C; *ν* (KBr) 3825–3104 cm^{-1} (OH); δ_H (400 MHz, CD_3OD): 0.75 (6H, t, *J*=7.4 Hz, 2×CH_3), 1.73–1.97 (4H, m, 2×CH_2), 4.95 (2H, br s, OH and NH), 6.93 (2H, s, CHCH); δ_C (100 MHz, CD_3OD, *T*=193 K): 8.5 (2C, 2×CH_3), 35.1 (2C, 2×CH_2), 76.2 (COH), 116.2, 127.8 (CHCH), 153.5 (NCN); *m*/*z* (DIP) 154 (M^+, 10%), 125 (100), 69 (81). HRMS (DIP) calcd for $C_8H_{14}N_2O$ 154.1106, found 154.1117.

4.5.2. Dicyclopropyl(1*H*-2-imidazolyl)methanol (4b). Obtained 0.50 g (93% yield) [recrystallisation (ethyl acetate/diethyl ether)]; pale yellow solid; mp 103–104 °C; *ν* (KBr) 3730–3158 cm^{-1} (OH); δ_H (300 MHz, CD_3OD): 0.29–0.34, 0.38–0.45, 1.31–1.40 (2H, 6H and 2H, respectively, 3m, 4×CH_2 and 2×CH ring), 5.28 (2H, br s, OH and NH), 6.91 (2H, s, NCHCHN); δ_C (75 MHz, CD_3OD): 0.9, 1.6 (4C, 4×CH_2), 20.8 (2C, 2×CH ring), 73.2 (COH), 121.9 (2C, NCHCHN), 153.9 (NCN); *m*/*z* (DIP) 179 (M^++1, 3%), 178 (15), 163 (19), 161 (12), 160 (11), 159 (43), 150 (15), 149 (30), 138 (14), 137 (100), 135 (37), 122 (13), 121 (26), 119 (10), 109 (25), 107 (18), 95 (56), 82 (29), 81 (11), 69 (64), 68 (14), 42 (13), 41 (22). HRMS (DIP) calcd for $C_{10}H_{14}N_2O$ 178.1106, found 178.1099.

4.5.3. 2-(1*H*-2-Imidazolyl)-2-adamantanol (4c). Obtained 0.59 g (91% yield) (product obtained after washing with ethyl acetate); white solid; mp 215–217 °C; *ν* (KBr) 3735–2985 cm^{-1} (OH); δ_H (300 MHz, DMSO-d_6): 1.48–1.52, 1.58–1.64, 1.78–1.83, 2.29–2.35 (2H, 5H, 3H and 4H, respectively, 4m, 5×CH_2 and 4×CH ring), 4.88 (1H, br s, OH), 6.77 and 6.97 (1H and 1H, 2s, NCHCHN), 11.60 (1H, br s, NH); δ_C (75 MHz, DMSO-d_6): 26.6, 26.8, 35.3 (4C, 4×CH ring), 32.2, 34.3, 37.6 (5C, 5×CH_2), 71.9 (COH), 115.4, 126.1 (NCHCHN), 152.5 (NCN); *m*/*z* (DIP) 222 (M^++4, 2%), 221 (17), 220 (100), 219 (27), 218 (6), 202 (31), 201 (20), 200 (22), 192 (27), 191 (10), 163 (12), 160 (10), 159 (12), 149 (10), 136 (20), 126 (11), 125 (11), 124 (12), 123 (10), 100 (14), 97 (22), 96 (33), 84 (12), 83 (25), 82 (11), 71 (13), 70 (17), 69 (11). HRMS (DIP) calcd for $C_{13}H_{18}N_2O$ 218.1419, found 218.1409.

4.5.4. 1-(1*H*-2-Imidazolyl)-1-phenylethanol (4d).[27] Obtained 0.31 g (55% yield) [recrystallisation (2-propanol)]; yellow solid; mp 168–170 °C; *ν* (KBr) 3695–3124 cm^{-1} (OH); δ_H (300 MHz, CD_3OD): 1.92 (3H, s, CH_3), 4.95 (2H, br s, OH and NH), 6.94 (2H, s, NCHCHN), 7.16–7.21, 7.24–7.29, 7.41–7.44 (1H, 2H and 2H, respectively, 3m, ArH); δ_C (75 MHz, CD_3OD): 30.0 (CH_3), 73.9 (COH), 122.3 (2C, NCHCHN), 126.2, 128.0, 129.1 (5C, 5×ArCH), 147.9 (ArC), 154.8 (NCN); *m*/*z* (DIP) 189 (M^++1, 6%), 188 (45), 187 (12), 174 (11), 173 (100), 170

(12), 169 (32), 155 (11), 145 (12), 111 (13), 105 (32), 95 (36), 77 (24), 69 (16), 43 (13).

4.5.5. 1-(1*H*-2-Imidazolyl)-2,2-dimethyl-1-propanol (4e).[33] Obtained 0.42 g (92% yield) [recrystallisation (ethanol)]; white solid; mp 237–238 °C; ν (KBr) 3736–3110 cm^{-1} (OH); δ_H (400 MHz, DMSO-d_6): 0.85 (9H, s, 3×CH_3), 4.25 (1H, s, C*H*OH), 5.45 (1H, br s, OH), 6.77, 6.94 (1H and 1H, 2s, CHCH), 11.64 (1H, br s, NH); δ_C (100 MHz, DMSO-d_6): 26.0 (3C, 3×CH_3), 35.5 [*C*(CH_3)$_3$], 75.1 (CHOH), 115.1, 126.5 (CHCH), 149.4 (NCN); *m*/*z* (DIP) 154 (M^+, 5%), 98 (100), 97 (85), 69 (12).

4.5.6. Cyclohexyl(1*H*-2-imidazolyl)methanol (4f).[34] Obtained 0.27 g (51% yield) [recrystallisation (ethanol/diethyl ether)]; white solid; mp 206–208 °C; ν (KBr) 3719–3120 cm^{-1} (OH); δ_H (400 MHz, DMSO-d_6): 0.85–1.14, 1.29–1.33, 1.56–1.74 (5H, 1H and 5H, respectively, 3m, 5×CH_2 and CH ring), 4.30 (1H, d, *J*=6.4 Hz, C*H*OH), 5.38 (1H, br s, OH), 6.78, 6.95 (1H and 1H, 2s, CHCH), 11.74 (1H, br s, NH); δ_C (100 MHz, DMSO-d_6): 25.8, 25.9, 26.3, 28.3, 28.9 (5×CH_2), 43.6 (CH ring), 71.9 (CHOH), 115.7, 126.7 (CHCH), 150.6 (NCN); *m*/*z* (DIP) 183 (M^++3, 1%), 182 (5), 181 (7), 180 (3), 100 (42), 99 (100), 98 (93), 97 (38), 70 (12), 69 (12), 55 (13), 43 (10), 41 (11).

4.5.7. 1*H*-2-Imidazolyl(phenyl)methanol (4g).[29] Obtained 0.31 g (59% yield) [recrystallisation (ethanol/diethyl ether)]; white solid; mp 192–194 °C; ν (KBr) 3656–2955 cm^{-1} (OH); δ_H (300 MHz, CD_3OD): 4.97 (2H, br s, OH and NH), 5.83 (1H, s, C*H*OH), 6.94 (2H, s, NCHCHN), 7.21–7.34, 7.39–7.42, (3H and 2H, respectively, 2m, ArH); δ_C (75 MHz, CD_3OD): 71.5 (CHOH), 122.5 (2C, NCHCHN), 127.5, 128.7, 129.4 (5C, 5×ArCH), 143.4 (ArC), 151.6 (NCN); *m*/*z* (DIP) 177 (M^++3, 9%), 176 (80), 175 (100), 174 (53), 173 (11), 158 (14), 157 (29), 156 (70), 155 (35), 147 (10), 146 (13), 129 (13), 105 (19), 99 (15), 98 (26), 97 (12), 95 (10), 80 (13), 79 (13), 78 (24), 77 (35), 71 (22), 70 (36), 69 (22), 51 (15).

4.5.8. 1*H*-2-Imidazolyl(4-methoxyphenyl)methanol (4h). Obtained 0.35 g (57% yield) [recrystallisation (ethanol/chloroform)]; white solid; mp 148–149 °C; ν (KBr) 3720–3124 cm^{-1} (OH); δ_H (300 MHz, CD_3OD): 3.75 (3H, s, CH_3), 4.83 (2H, br s, OH and NH), 5.78 (1H, s, C*H*OH), 6.86 (2H, d, *J*=8.7 Hz, ArH), 6.94 (2H, s, NCHCHN), 7.29 (2H, d, *J*=8.7 Hz, ArH); δ_C (75 MHz, CD_3OD): 55.7 (CH_3), 71.2 (CHOH), 114.8, 128.9 (4C, 4×ArCH), 122.6 (2C, NCHCHN), 135.6, 151.9, 160.8 (2×ArC and NCN); *m*/*z* (DIP) 207 (M^++3, 4%), 206 (24), 205 (62), 204 (64), 203 (22), 189 (11), 188 (15), 187 (19), 186 (35), 176 (15), 175 (13), 173 (15), 172 (26), 171 (100), 156 (13), 155 (14), 143 (15), 135 (36), 122 (15), 121 (35), 98 (13), 97 (19), 96 (12), 95 (20), 92 (11), 89 (11), 78 (10), 77 (21), 70 (19), 69 (28), 68 (12), 63 (10). HRMS (DIP) calcd for $C_{11}H_{12}N_2O_2$ 204.0899, found 204.0892.

4.5.9. 1*H*-2-Imidazolyl[4-(trifluoromethyl)phenyl]-methanol (4i). Obtained 0.42 g (58% yield) [recrystallisation (ethanol/chloroform)]; white solid; mp 184–186 °C; ν (KBr) 3660–3119 cm^{-1} (OH); δ_H (400 MHz, CD_3OD): 4.92 (2H, br s, OH and NH), 5.91 (1H, s, C*H*OH), 6.95 (2H, s, NCHCHN), 7.61 (4H, s, ArH); δ_C (100 MHz, CD_3OD): 70.7 (CHOH), 122.8 (2C, NCHCHN), 125.7 (q, *J*=271.3 Hz, CF_3), 126.3 (2C, m, 2×ArCH), 128.1 (2C, 2×ArCH), 130.8 (q, *J*=32.3 Hz, *C*CF_3), 147.9 (ArC), 150.9 (NCN); *m*/*z* (DIP) 245 (M^++3, 6%), 244 (56), 243 (100), 242 (68), 241 (17), 226 (10), 225 (22), 224 (61), 223 (18), 214 (10), 174 (10), 173 (22), 157 (12), 156 (16), 155 (39), 145 (29), 128 (19), 127 (19), 99 (12), 98 (22), 97 (15), 95 (12), 71 (15), 70 (34), 69 (32), 68 (12). HRMS (DIP) calcd for $C_{11}H_9F_3N_2O$ 242.0667, found 242.0659.

4.5.10. *N*-[1*H*-2-Imidazolyl(phenyl)methyl]aniline (4j). Obtained 0.36 g (48% yield) [recrystallisation (dichloromethane)]; white solid; mp 159–161 °C; ν (KBr) 3424 cm^{-1} (NH); δ_H (300 MHz, CD_3OD): 5.65 (1H, s, C*H*NH), 6.59–6.64, 7.02–7.07, 7.22–7.40 (3H, 2H and 5H, respectively, 3m, 10×ArH), 6.96 (2H, s, NCHCHN); δ_C (75 MHz, CD_3OD): 58.5 (CHNH), 114.7, 118.9, 128.4, 128.8, 129.8, 129.9 (10C, 10×ArCH), 122.8 (2C, NCHCHN), 142.1, 148.8, 150.7 (2×ArC and NCN); *m*/*z* (DIP) 252 (M^++3, 1%), 251 (7), 250 (19), 249 (19), 158 (56), 157 (100), 156 (23), 130 (12), 95 (18), 94 (57), 93 (61), 77 (21). HRMS (DIP) calcd for $C_{16}H_{15}N_3$ 249.1266, found 249.1262.

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