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Solvent-free direct regioselective ring opening of epoxides with imidazoles

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This paper is dedicated to Professor Dieter Enders on the occasion of his 60th birthday

Abstract—The reaction of different epoxides with commercially available imidazole at 60 °C leads to the formation of the corresponding 1-(β-hydroxyalkyl)imidazoles in a regioselective manner. When the reaction is applied to a chiral epoxide [(*R*)-styrene oxide], the expected chiral alcohol is isolated with the same enantiomeric excess. The use of benzimidazole as the heterocyclic component in the same process also allows the simple preparation of the corresponding 1-(β-hydroxyalkyl)benzimidazoles.

1. Introduction

Among heterocycles, 1,3-azoles are important compounds due to their extensive presence in naturally occurring products as well as many pharmacological and biological molecules.[1] The synthesis of this family of heterocyclic derivatives, mainly achieved either by ring closure reactions from different acyclic precursors or by substituent modification of heterocyclic systems, constitutes a wide field of interest in synthetic organic and medicinal research.[2] On the other hand, epoxides (straightforwardly prepared from the corresponding alkenes by an oxidation process[3]) can be considered as 'spring-loaded' rings for nucleophilic opening,[4] being versatile starting materials in organic synthesis:[5] the epoxide ring opening reaction is generally carried out under acidic or basic catalysis.[6] One especial case of 1,3-azoles are the corresponding 1-(2-hydroxyalkyl)imidazole and -benzimidazole derivatives, which have been considered to be of interest from a medicinal point of view due to their antifungal properties.[7] These products could be prepared by an epoxide ring opening reaction with imidazole nucleophiles, albeit harsh conditions (such as strong base/high temperature[8] or high pressure[9]) are required. Microwave-assisted ring opening of epoxides with nitrogen heterocycles[10] and Lewis acid [$Yb(OTf)_3$]-catalyzed ring opening reaction in the presence of an excess of epoxide (200 mol %)[11] have also been reported, these methodologies showing in our hands reproducibility problems. In addition, to the best of our knowledge, the use of benzimidazole as nucleophile in the ring opening of epoxides has only been reported using styrene oxide to give a moderate yield (45%) under strong basic conditions,[8] showing no reaction under high pressure conditions.[9] During our studies on the preparation of 2-(hydroxyalkyl)imidazoles by means of an isoprene-promoted lithiation of *N*-methylimidazole followed by reaction with carbonyl compounds,[12] we became interested in the synthesis of 1-(alkoxyalkyl) substituted imidazoles for the above commented reasons.[1] Herein, we describe the preparation of imidazolyl and benzimidazolyl alcohols by an epoxide ring opening with the free heterocycles under solvent-free conditions.

2. Results and discussion

Initially, we studied the reaction between imidazole (**1**) and styrene oxide (**2a**), the best result previously reported (70% of the product **3a**) being obtained using strong basic conditions.[8] The study for setting up the best reaction conditions is summarized in Table 1. According to some authors,[4,13] water is a unique environment for nucleophilic additions to epoxides favoring the demanding range of hydrogen-bonding situations, so recently Azizi and Saidi reported the aminolysis of epoxides by aliphatic and aromatic amines in water.[14] Therefore, our first trial was to carry out the reaction in water at 60 °C, which produced the imidazole derivative **3a** with a modest yield (36%, Table 1, entry 1), a longer reaction time (three days) giving a slight yield improvement (42%, Table 1, entry 2). 1-Phenyl-1,2-ethanediol was detected in small amounts as by-product in the reaction mixtures, possibly due to the competition of water as nucleophile. Then, we tried a solvent-free reaction: stirring the

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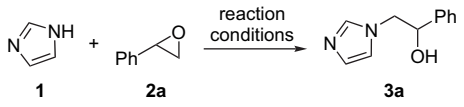
Table 1. Reaction conditions for styrene oxide (**2a**) ring opening with imidazole (Im; **1**)[a]



1 **2a** **3a**

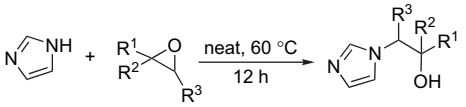
Entry	Equiv. of epoxide	Time (h)	Solvent ([Im])	T (°C)	Yield (%)[b]
1	1	12	H_2O (2.5 M)	60	36[c]
2	1	72	H_2O (2.5 M)	60	42[c]
3	1	12	Neat	60	76
4	1.5	12	Neat	60	66[d]
5	0.67	12	Neat	60	63[d]
6	1	12	Neat	24	34
7	1	48	Neat	24	68
8	1	10	Neat	100	70[d]
9	1	5	Neat	100	54
10	1	5	Neat	60	45
11	1	12	THF (2.5 M)	60	70
12	1	12	THF (0.25 M)	60	47
13	1	12	Acetone (2.5 M)	reflux	69

[a] Reaction carried out using 5 mmol of imidazole.
[b] Isolated yield of pure product after recrystallization.
[c] 1-Phenyl-1,2-ethanediol was detected in small amounts (<15%).
[d] The compound **3a** was purified by column chromatography (silica gel, mixtures of ethyl acetate and methanol).

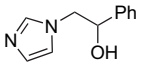
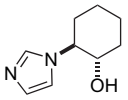
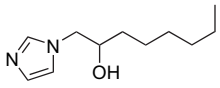
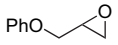
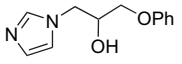
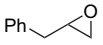
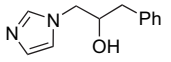
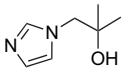
imidazole (**1**) and the epoxide **2a** (1:1 ratio) in the absence of any solvent at 60 °C produced the corresponding compound **3a** in 76% yield (Table 1, entry 3), which was directly recrystallized from the reaction mixture. The use of an excess either of the epoxide or imidazole did not give better results, in both cases the purification of compound **3a** being more difficult (Table 1, entries 4 and 5, respectively, and footnote d). Changing the temperature to room temperature slowed the reaction down, so a reaction time of two days was needed in order to achieve a similar yield (Table 1, entry 7), lower yield (34%) of the imidazole derivative being obtained after 12 h (Table 1, compare entries 3 and 6). Carrying out the process at higher temperature (100 °C) gave a slightly faster reaction (compare the yields after 5 h, Table 1, entries 9 and 10), albeit no higher yield was obtained when the reaction was completed (Table 1, entry 8). The reaction mixture became a dense slurry at the end, thus we thought that a dispersion medium might help to improve the yield of the final product. However, the use of a small amount of a solvent such as THF or acetone was shown to have no influence on the outcome of the reaction, producing the resultant compound **3a** with a yield comparable to that of the solvent-free reaction (Table 1, compare entries 3, 11, and 13). Nevertheless, lower concentration of the reagents gave the corresponding product **3a** with lower yield (Table 1, entry 12).

Once we knew the optimal reaction conditions, we considered different epoxides so, unless otherwise stated, an equimolecular mixture of imidazole (**1**) and an epoxide **2** was heated at 60 °C for 12 h in the absence of any solvent, and the corresponding product was isolated by recrystallization (or in some cases by column chromatography, see Section 4). As presented in Table 2, all the examined substrates **2** were transformed into the corresponding imidazolyl alcohol derivatives **3** with good isolated yields, being possible to carry out the reaction in gram scale (20 mmol; see Table 2 and Section 4). In all cases, the nucleophile attack occurred

Table 2. Ring opening of epoxides **2** with imidazole (**1**) under solvent-free conditions[a]

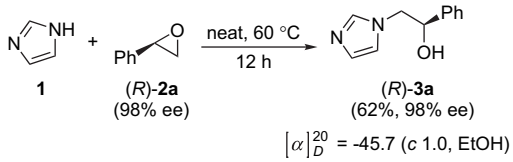


1 **2** **3**

Entry	Epoxide	Product		
		No.	Structure	Yield (%)[b]
1	 (**2a**)	**3a**		76
2	 (**2b**)	**3b**		84
3	 (**2c**)	**3c**		92
4	 (**2d**)	**3d**		82
5	 (**2e**)	**3e**		81[c]
6[d]	 (**2f**)	**3f**		72[c]

[a] Reaction performed by mixing imidazole (**1**; 20 mmol) and the epoxide **2** (20 mmol) and heating at 60 °C for 12 h.
[b] Isolated yield of pure product after recrystallization.
[c] Purification was done by column chromatography (silica gel, mixtures of ethyl acetate and methanol).
[d] Reaction was carried out at 45 °C.

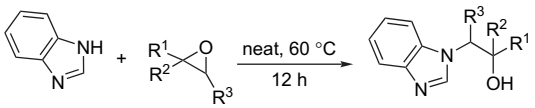
only at the less hindered carbon atom of the epoxide, which is consistent with an S_N2 mechanism. Consequently, performing the reaction with (*R*)-styrene oxide produced the corresponding (*R*)-2-(1-imidazolyl)-1-phenylethanol [(*R*)-**3a**] in 62% yield and the same enantiomeric excess as the starting epoxide (98% ee, determined by HPLC analysis using DAICEL CHIRALCEL OD-H column, Scheme 1). As expected, for cyclohexene oxide (**2b**), the corresponding *trans*-product **3b** was the only reaction product isolated (Table 2, entry 2).



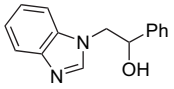
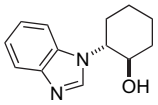
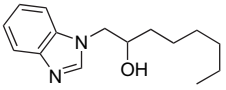
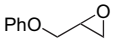
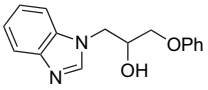
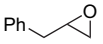
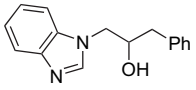
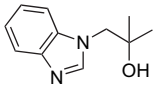
Scheme 1. Ring opening of (*R*)-styrene oxide [(*R*)-**2a**] with imidazole (**1**) under solvent-free conditions.

In the second part of this work we studied the ring opening using benzimidazole, which normally reacts less effectively than imidazole. Therefore, heating an equimolecular mixture of benzimidazole (**4**) and different epoxides (**2**) at 60 °C produced after 12 h the corresponding alcohol derivatives **5** (Table 3). These reaction conditions allowed to prepare the corresponding benzimidazole derivatives in gram scale

Table 3. Ring opening of epoxides **2** with benzimidazole (**4**) under solvent-free conditions[a]



4 **2** **5**

Entry	Epoxide	Product		
		No.	Structure	Yield (%)[b]
1	 (**2a**)	**5a**		62[c]
2	 (**2b**)	**5b**		74
3	 (**2c**)	**5c**		86
4	 (**2d**)	**5d**		71
5	 (**2e**)	**5e**		66
6[d]	 (**2f**)	**5f**		35[c,e]

[a] Reaction performed by mixing benzimidazole (**4**; 20 mmol) and the epoxide **2** (20 mmol) and heating at 60 °C for 12 h.
[b] Isolated yield of pure product after recrystallization.
[c] Purification was done by column chromatography (silica gel, mixtures of ethyl acetate and methanol).
[d] Reaction was carried out at 45 °C.
[e] Low yield due to the volatility of the starting epoxide.

with moderate to good isolated yields (Table 3), being a little bit lower than for the corresponding imidazole derivatives. As it happened above, the heterocyclic ring opened the epoxides by a regioselective nucleophilic attack to the less hindered carbon atom.

3. Conclusions

The chemistry described here is a versatile and useful methodology, whose principal characteristics are (a) the use of easily available materials, (b) no need of any catalyst or solvent for the reaction, and (c) very mild reaction conditions and remarkable simplicity in the manipulation of the reaction and work-up, allowing to carry out the reaction in gram scale.

4. Experimental

4.1. General

All commercially available reagents (Acros, Aldrich, Fluka) were used without further purification. 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) parts per million and coupling constants (J) in hertz. 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 a modality of direct insertion probe (DIP). The chromatographic analyses (GLC) were performed with an Agilent 6890N instrument equipped with a flame ionization 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. Column chromatography was performed using silica gel of 40 μm (J. T. Baker, pH=6.7–7.3 of 10% aqueous suspension). Thin-layer chromatography was carried out on TLC plastic sheets with silica gel 60 F_{254} (Merck). HPLC analyses were performed on a Shimadzu LC-10AD equipped with the chiral column Chiralcel OD-H, using mixtures of *n*-hexane/isopropyl alcohol as mobile phase. Optical rotations were measured on a Perkin Elmer 341 polarimeter.

4.2. General procedure for the ring opening of epoxides with imidazole

A mixture of imidazole (20 mmol, 1.38 g) and epoxide (20 mmol) was placed in a round bottom flask and stirred at 60 °C (except for the epoxide **2f**: carried out at 45 °C) for 12 h. The resulting mixture was purified by recrystallization (normally using acetone/hexane or dichloromethane/hexane) and/or by column chromatography (silica gel, mixtures of ethyl acetate and methanol from 20:1 to 30:1) to yield the corresponding imidazolyl alcohols **3**. Yields are included in Table 2, physical, spectroscopic, and analytical data, as well as literature references for known compounds, follow.

4.2.1. 2-(1*H*-Imidazol-1-yl)-1-phenylethanol (3a).[9] White solid; mp 146–147 °C (acetone/hexane); t_R 13.78; ν (KBr) 3689–2955 cm^{-1} (OH); δ_H (400 MHz, $CDCl_3$): 3.47 (1H, s, OH), 4.11 (2H, m, CH_2), 4.88 (1H, m, C*H*OH), 6.89, 6.92 (1H and 1H, 2s, NCHCHN), 7.27–7.38 (6H, m, ArH and NCHN); δ_C (100 MHz, $CDCl_3$): 54.4 (CH_2), 73.0 (CHOH), 119.9, 125.7, 127.9, 128.0, 128.5 (7C, ArCH and NCHCHN), 137.4 (NCHN), 140.9 (ArC); m/z 189 (M^++1, 2%), 188 (15), 107 (24), 82 (100), 81 (45), 79 (39), 77 (28).

4.2.2. *trans*-2-(1*H*-Imidazol-1-yl)cyclohexanol (3b).[9] White solid; mp 132–133 °C (acetone/hexane); t_R 12.26; ν (KBr) 3702–2975 cm^{-1} (OH); δ_H (300 MHz, CD_3OD): 1.41, 1.82, 2.01–2.09 (3H, 3H, and 2H, respectively, 3m, 4×CH_2), 3.63, 3.78 (1H and 1H, 2m, 2×CH cyclohexane ring), 6.95, 7.18 (1H and 1H, 2s, NCHCHN), 7.67 (1H, s, NCHN); δ_C (75 MHz, CD_3OD): 25.4, 26.2, 33.7, 35.9 (4×CH_2), 64.6 (CHN cyclohexane ring), 73.9 (CHOH), 118.8, 128.6 (NCHCHN), 137.9 (NCHN); m/z 167 (M^++1,

14%), 166 (100), 139 (15), 137 (10), 109 (16), 107 (12), 98 (14), 96 (11), 95 (60), 83 (11), 82 (49), 81 (30), 79 (10), 70 (11), 69 (68), 68 (41), 67 (12), 55 (12), 53 (11).

4.2.3. 1-(1*H*-Imidazol-1-yl)-2-octanol (3c). Dense pale yellow oil; t_R 13.21; ν (film) 3770–3005 cm^{-1} (OH); δ_H (400 MHz, $CDCl_3$): 0.88 (3H, m, CH_3), 1.23–1.39, 1.40–1.52 (7H and 3H, respectively, 2m, 5×CH_2), 3.80 (2H, m, NCH_2), 3.93 (1H, m, C*H*OH), 5.46 (1H, br s, OH), 6.85, 6.90 (1H and 1H, 2s, NCHCHN), 7.34 (1H, s, NCHN); δ_C (100 MHz, $CDCl_3$): 14.1 (CH_3), 22.6, 25.7, 29.3, 31.8, 34.6 (5×CH_2), 53.7 (NCH_2), 70.5 (CHOH), 119.8, 128.3 (NCHCHN), 137.5 (NCHN); *m/z* 197 (M^++1, 3%), 196 (16), 169 (11), 82 (100), 81 (47), 69 (19), 55 (24). HRMS calcd for $C_{11}H_{20}N_2O$ 196.1576, found 196.1565.

4.2.4. 1-(1*H*-Imidazol-1-yl)-3-phenoxy-2-propanol (3d).[11] Dense colorless oil; t_R 15.16; ν (film) 3716–2988 cm^{-1} (OH); δ_H (400 MHz, $CDCl_3$): 3.80, 3.97, 4.05, 4.18–4.21 (1H, 1H, 1H, and 2H, respectively, 3dd, *J*=9.3, 6.8 Hz, *J*=9.3, 4.6 Hz, *J*=14.8, 7.7 Hz and 1m, respectively, 2×CH_2 and C*H*OH), 6.85–6.97, 7.26 (5H and 2H, respectively, 2m, ArH and NCHCHN), 7.39 (1H, s, NCHN); δ_C (100 MHz, $CDCl_3$): 50.5 (NCH_2), 68.5 (CHOH), 68.6 (OCH_2), 114.5, 120.2, 121.3, 128.1, 129.6 (7C, ArCH and NCHCHN), 137.7 (NCHN), 158.2 (ArC); *m/z* 219 (M^++1, 15%), 218 (100), 125 (15), 107 (20), 94 (26), 82 (96), 81 (62), 77 (28), 55 (10), 54 (14). HRMS calcd for $C_{12}H_{14}N_2O_2$ 218.1055, found 218.1073.

4.2.5. 1-(1*H*-Imidazol-1-yl)-3-phenyl-2-propanol (3e). Colorless oil; t_R 14.49; ν (film) 3745–2973 cm^{-1} (OH); δ_H (300 MHz, $CDCl_3$): 2.70 (1H, dd, *J*=13.7, 5.9 Hz, CH*H*Ph), 2.80 (1H, dd, *J*=13.7, 7.3 Hz, C*H*HPh), 3.77 (1H, dd, *J*=14.0, 7.9 Hz, NC*H*H), 3.92 (1H, dd, *J*=14.0, 2.8 Hz, NCH*H*), 4.02 (1H, m, C*H*OH), 5.24 (1H, br s, OH), 6.77, 6.85 (1H and 1H, 2s, NCHCHN), 7.18–7.32 (6H, m, ArH and NCHN); δ_C (75 MHz, $CDCl_3$): 41.2 (CH_2Ph), 52.5 (NCH_2), 71.3 (CHOH), 119.7, 126.5 (NCHCHN), 128.1, 128.5, 129.3 (5C, ArCH), 137.3 (NCHN), 137.6 (ArC); *m/z* 203 (M^++1, 8%), 202 (49), 184 (23), 121 (14), 117 (30), 103 (31), 92 (12), 91 (62), 83 (13), 82 (100), 81 (52), 77 (12), 65 (16), 55 (12), 54 (11). HRMS calcd for $C_{12}H_{14}N_2O$ 202.1106, found 202.1110.

4.2.6. 1-(1*H*-Imidazol-1-yl)-2-methyl-2-propanol (3f). Dense amber oil; t_R 9.15; ν (film) 3722–3015 cm^{-1} (OH); δ_H (400 MHz, $CDCl_3$): 1.63 (6H, s, 2×CH_3), 4.14 (1H, br s, OH), 4.26 (2H, s, CH_2), 7.33 (2H, s, CHCH), 7.85 (1H, s, NCHN); δ_C (100 MHz, $CDCl_3$): 27.2 (2C, 2×CH_3), 58.2 (CH_2), 69.8 (COH), 120.8, 128.1 (CHCH), 138.2 (NCHN); *m/z* 141 (M^++1, 3%), 140 (36), 125 (13), 82 (100), 81 (72), 59 (58), 55 (12), 54 (14). HRMS calcd for $C_7H_{12}N_2O$ 140.0950, found 140.0947.

4.3. (*R*)-2-(1*H*-Imidazol-1-yl)-1-phenylethanol [(*R*)-3a][15]

A mixture of imidazole (2 mmol, 0.138 g) and (*R*)-styrene oxide (2 mmol, 0.236 mL) was placed in a round bottom flask and stirred at 60 °C for 12 h. The resulting mixture was purified by recrystallization (acetone/hexane) giving 0.233 g (62% yield) of a white solid; $[\alpha]_D^{20}$ −45.7 (*c* 1.0, EtOH, 98% ee from HPLC) [lit.[15] $[\alpha]_D^{25}$ −47.6 (*c* 1.0, EtOH)]; δ_H (400 MHz, $CDCl_3$): 3.25 (1H, s, OH), 4.10 (2H, m, CH_2), 4.88 (1H, m, C*H*OH), 6.89, 6.92 (1H and 1H, 2s, NCHCHN), 7.27–7.37 (6H, m, ArH and NCHN); δ_C (100 MHz, $CDCl_3$): 54.5 (CH_2), 73.1 (CHOH), 120.0, 125.7, 128.0, 128.1, 128.5 (7C, ArCH and NCHCHN), 137.5 (NCHN), 140.9 (ArC). The enantiomeric excess was determined by chiral HPLC: Daicel Chiralcel OD-H, λ=210 nm, *n*-hexane/2-propanol (90/10), 1 mL/min, t_R=40.15 min.

4.4. General procedure for the ring opening of epoxides with benzimidazole

A mixture of benzimidazole (20 mmol, 2.40 g) and epoxide (20 mmol) was placed in a round bottom flask and stirred at 60 °C (except for the epoxide **2f**: carried out at 45 °C) for 12 h. The resulting mixture was purified by recrystallization (normally using acetone/hexane) and/or by column chromatography (silica gel, mixtures of ethyl acetate and methanol from 20:1 to 30:1) to yield the corresponding products **5**. Yields are included in Table 3, physical, spectroscopic, and analytical data, as well as literature references for known compounds, follow.

4.4.1. 2-(1*H*-Benzimidazol-1-yl)-1-phenylethanol (5a).[8] Amber solid; mp 88–89 °C (acetone/hexane); t_R 16.72; ν (KBr) 3725–2963 cm^{-1} (OH); δ_H (400 MHz, $CDCl_3$): 4.19 (1H, dd, *J*=14.4, 8.3 Hz, CH*H*), 4.26 (1H, dd, *J*=14.4, 3.5 Hz, C*H*H), 5.04 (1H, dd, *J*=8.3, 3.5 Hz, C*H*OH), 5.80 (1H, br s, OH), 7.07–7.42, 7.56 (9H and 1H, respectively, m and s, respectively, ArH and NCHN); δ_C (100 MHz, $CDCl_3$): 53.1 (CH_2), 72.0 (CHOH), 109.7, 119.7, 122.2, 123.0, 126.0, 128.3, 128.8 (9C, ArCH), 133.6, 141.4, 142.8 (ArC), 143.7 (NCHN); *m/z* 239 (M^++1, 5%), 238 (29), 132 (100), 131 (74), 107 (16), 104 (11), 79 (19), 77 (30).

4.4.2. *trans*-2-(1*H*-Benzimidazol-1-yl)cyclohexanol (5b). Beige solid; mp 164–165 °C (acetone/hexane); t_R 15.55; ν (KBr) 3702–2982 cm^{-1} (OH); δ_H (300 MHz, $CDCl_3$): 1.41–1.63, 1.73–1.93, 2.01–2.06, 2.24–2.28 (3H, 3H, 1H, and 1H, 4m, 4×CH_2), 3.92–4.05 (2H, m, 2×CH ring), 7.08–7.13, 7.19–7.24, 7.42–7.46 (1H, 1H, and 3H, 3m, ArH and NCHN); δ_C (300 MHz, $CDCl_3$): 24.5, 25.3, 31.9, 34.4 (4×CH_2), 62.5 (CHN ring), 72.2 (CHOH), 110.6, 119.4, 122.1, 122.6 (ArCH), 133.8, 142.8 (ArC), 140.7 (NCHN); *m/z* 218 (M^++2, 1%), 217 (15), 216 (100), 187 (14), 159 (32), 157 (32), 145 (49), 132 (60), 131 (23), 119 (28), 118 (45). HRMS calcd for $C_{13}H_{16}N_2O$ 216.1263, found 216.1264.

4.4.3. 1-(1*H*-Benzimidazol-1-yl)-2-octanol (5c). Beige solid; mp 61–62 °C (ether); t_R 16.22; ν (KBr) 3725–3009 cm^{-1} (OH); δ_H (300 MHz, $CDCl_3$): 0.90 (3H, m, CH_3), 1.32–1.59 (10H, m, 5×CH_2), 3.93–4.00, 4.17 (2H and 1H, respectively, 2m, NCH_2 and C*H*OH), 4.97 (1H, br s, OH), 7.06, 7.17 (1H and 1H, 2m, ArH), 7.31, 7.39 (1H and 1H, 2d, *J*=8.1 Hz, ArH), 7.64 (1H, s, NCHN); δ_C (75 MHz, $CDCl_3$): 14.0 (CH_3), 22.6, 25.7, 29.2, 31.7, 34.7 (5×CH_2), 51.6 (NCH_2), 69.6 (CHOH), 109.6, 119.5, 122.0, 122.7 (ArCH), 133.6, 142.8 (ArC), 143.5 (NCHN); *m/z* 247 (M^++1, 6%), 246 (31), 133 (11), 132 (100), 131 (77), 119 (17), 104 (13), 77 (12). HRMS calcd for $C_{15}H_{22}N_2O$ 246.1732, found 246.1721.

4.4.4. 1-(1*H*-Benzimidazol-1-yl)-3-phenoxy-2-propanol (5d). White solid; mp 148–149 °C (ethanol/acetone); t_R 18.10; ν (KBr) 3700–2984 cm^{-1} (OH); δ_H (300 MHz, CD_3OD): 3.92, 3.99, 4.27–4.35, 4.42, 4.55 (1H, 1H, 1H, 1H, and 1H, 2dd, J=9.7, 5.6 Hz, J=9.8, 5.0 Hz, 1m and 2dd, J=14.4, 7.2 Hz, J=14.4, 3.8 Hz, respectively, 2×CH_2 and C*H*OH), 6.93–6.97, 7.23–7.31, 7.56–7.70 (3H, 4H, and 2H, respectively, 3m, ArH), 7.57 (1H, s, NCHN); δ_C (75 MHz, CD_3OD): 48.8 (NCH_2), 69.4 (CHOH), 70.3 (OCH_2), 111.7, 115.6, 120.1, 122.2, 123.4, 124.2, 130.6 (9C, ArCH), 135.4, 143.9, 160.0 (ArC), 145.7 (NCHN); *m/z* 271 (M^++3, 1%), 270 (11), 269 (46), 268 (75), 133 (21), 132 (69), 130 (100), 104 (14), 77 (29). HRMS calcd for $C_{16}H_{16}N_2O_2$ 268.1212, found 268.1237.

4.4.5. 1-(1*H*-Benzimidazol-1-yl)-3-phenyl-2-propanol (5e). White solid; mp 126–127 °C (acetone/hexane); t_R 17.48; ν (KBr) 3689–2975 cm^{-1} (OH); δ_H (300 MHz, $CDCl_3$): 2.84, 2.92 (1H and 1H, 2dd, J=13.9, 6.2 Hz, J=13.7, 7.5 Hz, CH_2), 3.99, 4.13–4.23 (1H and 2H, respectively, dd, J=14.2, 8.6 Hz, and 1m, respectively, NCH_2 and C*H*OH), 7.06–7.37 (9H, m, ArH), 7.59 (1H, s, NCHN); δ_C (75 MHz, $CDCl_3$): 41.5 (CH_2), 50.6 (NCH_2), 70.6 (CHOH), 109.6, 119.6, 122.0, 122.7, 126.8, 128.7, 129.3 (9C, ArCH), 133.6, 137.5, 142.8 (ArC), 143.5 (NCHN); *m/z* 254 (M^++2, 2%), 253 (16), 252 (86), 133 (14), 132 (100), 131 (97), 121 (13), 104 (17), 103 (16), 91 (24), 77 (21). HRMS calcd for $C_{16}H_{16}N_2O$ 252.1263, found 252.1278.

4.4.6. 1-(1*H*-Benzimidazol-1-yl)-2-methyl-2-propanol (5f). Pale yellow solid; mp 144–145 °C (ethyl acetate/methanol); t_R 12.97; ν (KBr) 3725–2999 cm^{-1} (OH); δ_H (400 MHz, $CDCl_3$): 1.30 (6H, s, 2×CH_3), 4.12 (2H, s, CH_2), 7.21–7.30, 7.44, 7.74 (2H, 1H, and 1H, 3m, ArH), 7.94 (1H, s, NCHN); δ_C (75 MHz, $CDCl_3$): 27.5 (2C, 2×CH_3), 55.4 (CH_2), 70.9 (COH), 110.3, 119.7, 121.9, 122.9 (ArCH), 134.6, 142.7 (ArC), 144.2 (NCHN); *m/z* 191 (M^++1, 7%), 190 (45), 132 (87), 131 (100), 104 (14), 77 (16), 59 (30). HRMS calcd for $C_{11}H_{14}N_2O$ 190.1106, found 190.1111.

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