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Metal catalyst-free *N*-Allylation/alkylation of Imidazole and Benzimidazole with Morita–Baylis–Hillman (MBH) alcohols and acetates

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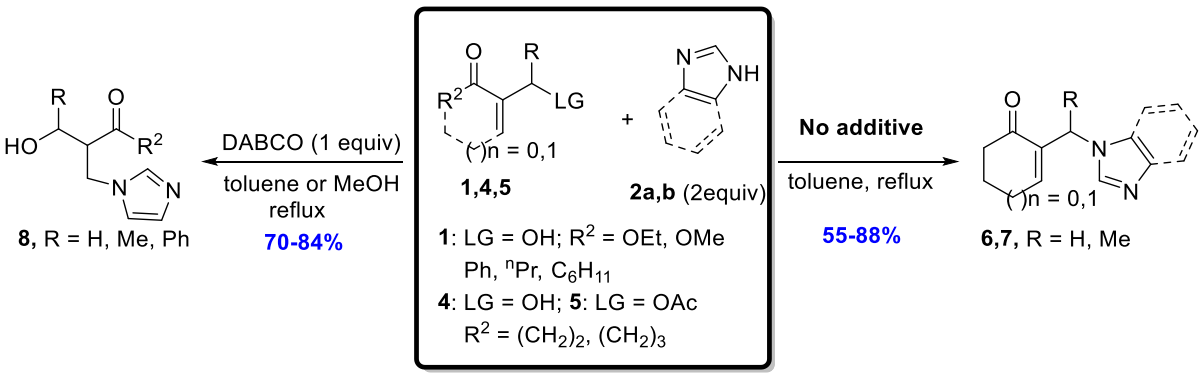
ABSTRACT: A highly α-regioselective *N*-nucleophilic allylic substitutions of cyclic MBH alcohols and acetates with imidazole or benzimidazole, in toluene at reflux with an azeotropic distillation, was successfully carried out with no catalysts or additives, affording the corresponding *N*-substituted imidazole derivatives in good yields. On the other hand, in refluxing toluene or methanol, the aza-Michael additions of imidazole onto acyclic MBH alcohols was performed using DABCO as an additive, leading to the corresponding 1,4-adducts in 70-84% yields.



Keywords: Morita–Baylis–Hillman; imidazole; allylic substitution; aza-Michael addition.

INTRODUCTION

Morita–Baylis–Hillman (MBH) adducts are multi-functionalized compounds having both hydroxyl moiety and Michael acceptor unit. They have been found as valuable synthons and useful precursors for the synthesis of various biologically active molecules.[1] Recently, MBH adducts, as electrophilic substrates, have been

employed to achieve fruitful results in allylic substitution reactions with various nucleophiles, including *C*- and heteronucleophiles, such as compounds bearing –OH, –SH and –NH groups.[2] Among them, the carbon–nitrogen bond formation through *N*-nucleophilic substitutions plays a very useful role for the synthesis of numerous compounds exhibiting various biological activities.[1,2]

In this context, imidazole moiety is widely known as one of the most group which plays efficient roles in bioactive compounds.[3] For instance, a number of *N*-substituted imidazole derivatives, such as miconazole, ketoconazole, genaconazole, and bifonazole have become well-established drugs for the treatment of numerous mycotic infections (Figure 1).[4] Therefore, the development of new methods for the preparation of such compounds is highly required.

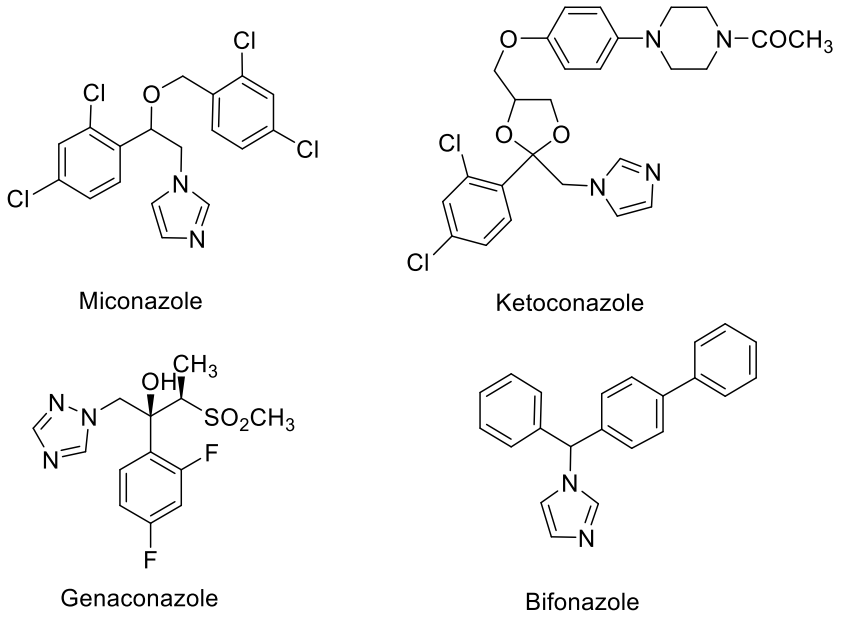
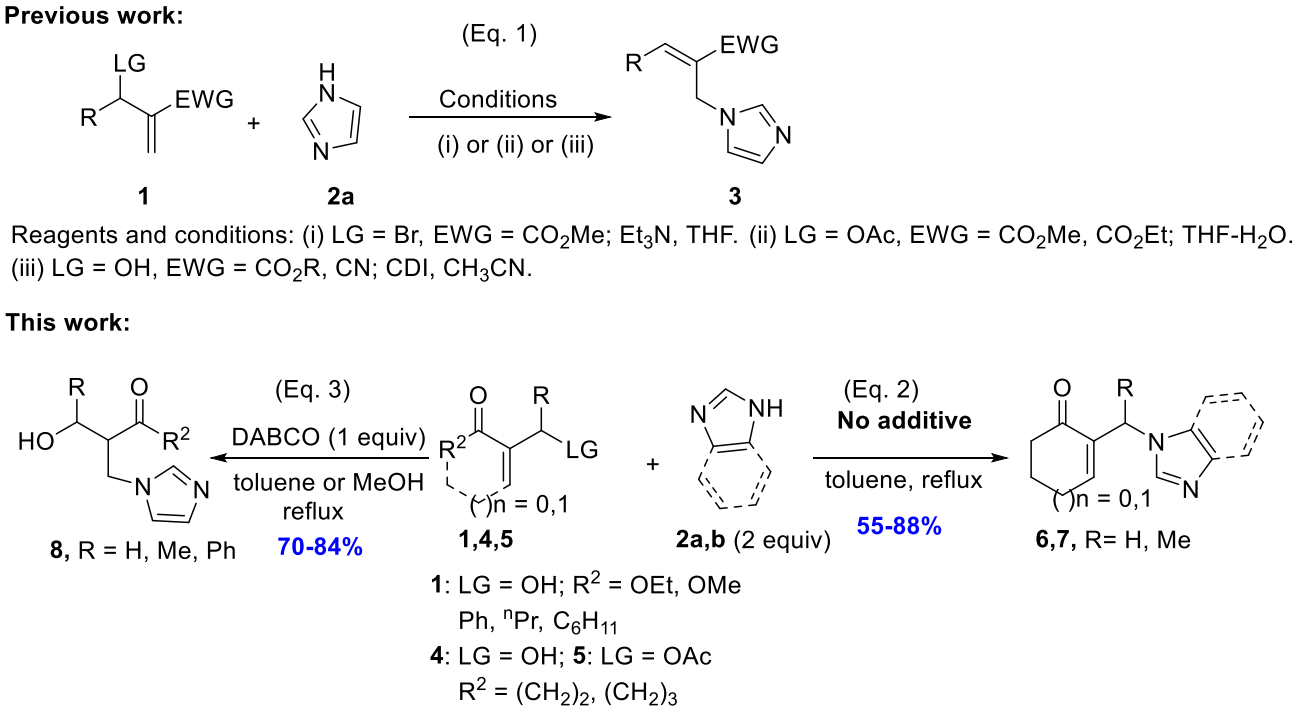


Figure 1. Medicines containing imidazole nucleus

The MBH acetates, instead of the corresponding alcohols, have been extensively used as precursors in the nucleophilic allylic substitutions with amines, presumably due to the perceived poor leaving group ability and low reactivity of the hydroxyl moiety. Interestingly, the direct nucleophilic substitutions of the corresponding alcohols have drawn much attention because of the availability of these substrates and the formation of water as the sole non-toxic by-product in the reaction.[5] In general, the previous methods for the amination of MBH alcohols needed catalysts or additives such as $FeCl_3$,[6] $In(OTf)_3$,[7] $MoCl_5$[8], $AuCl_3$,[9] and I_2[10] as Lewis acids.

Alternatively, Yang et al.[11] have developed a catalytic system involving Pd/Ti(O^iPr)$_4$ or Pd/carboxylic acid for the direct allylation of anilines with alcohols.

The synthesis of *N*-allylation imidazole derivatives **3** has been previously carried out using acyclic MBH adducts bearing good leaving groups such as bromide derivatives in Et_3N-THF,[12] (Scheme 1, eq.1 (i)) and acetates in THF-water,[13] (Scheme 1, eq.1 (ii)), or MBH alcohols in the presence of CDI (i.e., 1,1'-carbonyl diimidazole) in acetonitrile (Scheme 1, eq.1, (iii)).[14] In the last case, as the hydroxyl moiety is not a good leaving group, such alcohols were *in situ* converted into the corresponding *O*-allyl carbamates as leaving groups, followed by their reaction with imidazoles, affording the S_N2' products **3** (Scheme 1, eq. 1, iii)).



Scheme 1. Synthesis of *N*-substituted imidazole derivatives from MBH adducts

Correlatively, we have previously reported a direct amination of cyclic MBH alcohols **4** with morpholine in the presence of imidazole **2a**, as a powerful nucleophilic additive, affording, *via* competitive allylic nucleophilic substitutions in toluene at reflux, a mixture of the corresponding *N*-substituted morpholine and *N*-substituted imidazole derivatives **6**.[15] In addition, the literature survey showed that nucleophilic allylic substitutions of acyclic/cyclic MBH adducts **1**,**4**,**5**, bearing good or poor leaving groups, using imidazole derivatives, as nucleophilic reagents,

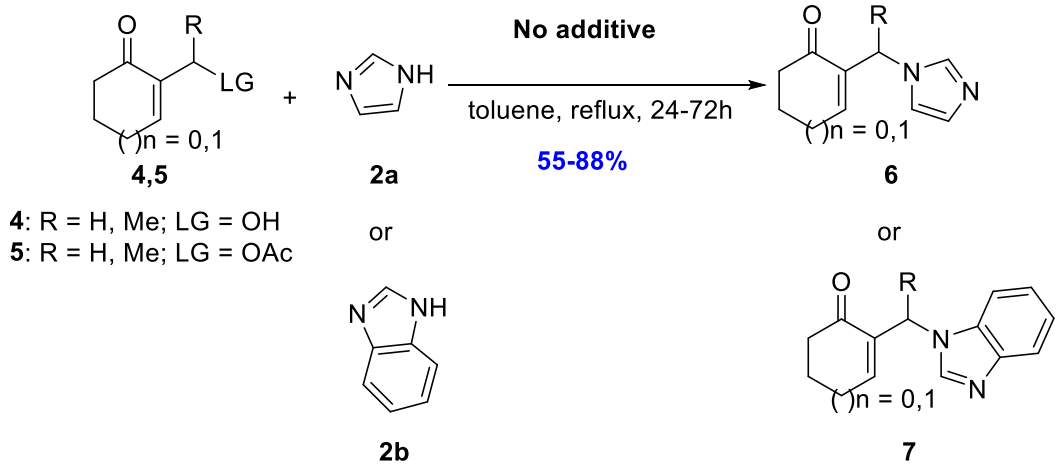
has not been extensively developed. Therefore, in continuation of our previous study on nucleophilic allylic substitutions of MBH adducts,[15-18] we disclose in this work a simple efficient procedure for the synthesis of *N*-substituted imidazoles **6-8**, either through direct conversions of the corresponding cyclic MBH alcohols **4** as well as acetates **5**, in the presence of imidazoles **2a,b**, as nucleophilic reagents, without catalysts or activating agents (Scheme 1, equation 2), or from acyclic MBH alcohols **1,** using DABCO, as a powerful nucleophilic additive (Scheme 1, equation 3).

■ RESULTS AND DISCUSSION

In our first investigations, we selected the reaction of the primary acetate **5a**, as the model substrate bearing a good leaving group, with imidazole **2a** (2 equiv), as a powerful nucleophilic reagent. The reaction was achieved with no need of a catalyst or any additive, in toluene at reflux, affording within 24 h the S_N2-ty*pe* product **6a** in 82% yield (Table 1, entry 1). Similarly, the five-membred acetate **5b** reacted, under the same conditions, and gave the *N*-allylic imidazole **6b** in 65% yield (Table 1, entry 2).

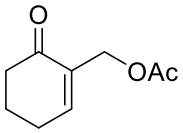
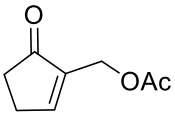
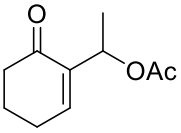
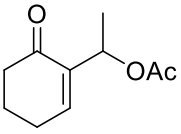
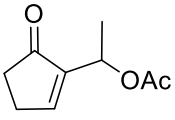
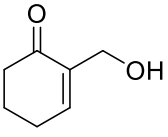
Futhermore, treatment of secondary acetates **5c,d** with imidazoles **2a,b** (2 equiv) in refluxing toluene, afforded the *N*-substituted imidazoles **6c**,**d** and **7a** within ca. 24 h in 69-87% yields (Table 1, entries 3-5).

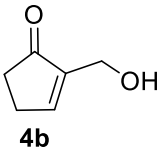
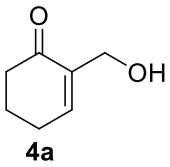
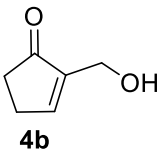
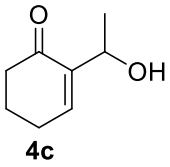
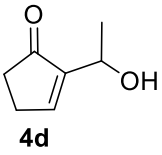
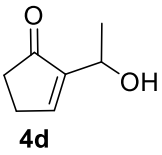
Table 1. Allylation of imidazole derivatives **2a**,**b** with cylic MBH adducts **4**,**5**



4: R = H, Me; LG = OH
5: R = H, Me; LG = OAc

97
98

Entry	MBH adduct **4** or **5**	Imidazole **2a** or **2b**	Time (h)	Product **6** or **7**	Yield (%) **6** or **7**
1	 **5a**	**2a**	24	**6a**	82
2	 **5b**	**2a**	24	**6b**	65
3	 **5c**	**2a**	24	**6c**	75
4	 **5c**	**2b**	48	**7a**	87
5	 **5d**	**2a**	24	**6d**	69
6	 **4a**	**2a**	48	**6a**	88

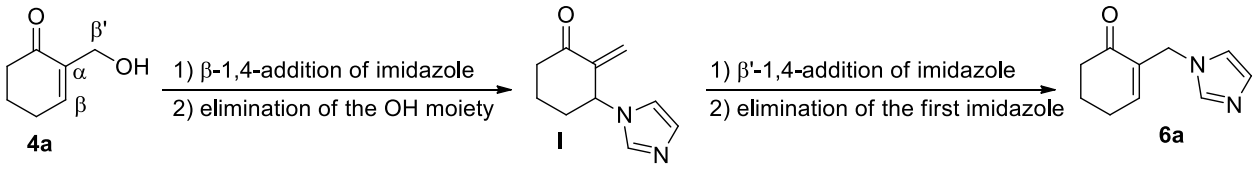
7	 4b	**2a**	24	**6b**	55
8	 4a	**2b**	72	**7b**	80
9	 4b	**2b**	72	**7c**	72
10	 4c	**2a**	48	**6c**	76
11	 4d	**2a**	24	**6d**	60
12	 4d	**2b**	72	**7d**	85

Having established the optimized conditions for the amination of primary and secondary acetates **5a-d** (Table 1, entries 1-5), carrying a good leaving group (OAc), we turned our attention to the investigation of the direct amination of MBH alcohols **4a-d**, with a poor leaving group (OH). Under the previous conditions (2 equiv of imidazole, toluene, reflux), the conversion of alcohol **4a** into the corresponding imidazole **6a** was very slow and the starting materials were almost recovered. However, the continuous removal of water, obtained from the direct amination of alcohol **4a,** by azeotropic distillation, shifts the position of equilibrium in the direction of the formation of the allylation imidazole **6a** in 88% good yield (Table 1, entry 6).

This protocol was also successfully extended to the reaction of the primary five-membered alcohol **4b** with imidazole **2a** as well as to that of alcohols **4a**,**b** with benzimidazole **2b**, leading to the S_N2-type products **6b** and **7b,c**, respectively, in 55-80% yields (Table 1, entries 7-9).

In addition, we have shown that the direct amination of secondary alcohols **4c-d** could be achieved with imidazole derivatives **2a,b**, under the conditions established above, affording, within 24-72h, the allylation products **6c,d** and **7d** in 60-85% yields (Table 1, entries 10-12).

Mechanistically, we believe that the nucleophilic allylic substitutions of alcohols **4**, such as **4a**, starts with a conjugate addition of imidazole **2a** at the C_β position of the Michael acceptor **4a**, followed by elimination of the hydroxyl moiety, affording the intermediate **I**. Similarly, a further second β'-conjugate addition of imidazole **2a** to **I** might occur, followed by elimination of imidazole **2a,** providing finally the allylic derivative **6a** (Scheme 2).[16,19] It is notable that such reaction mechanism, involving the intermediate **I**, was previously explored by Smith[20] and supported by Tamura studies.[21]

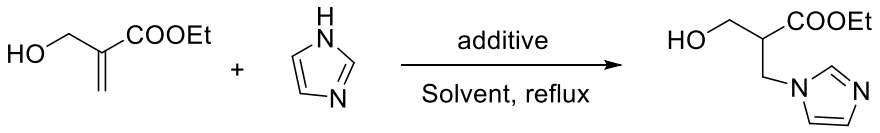


Scheme 2. Proposed mechanism for the allylation of imidazole with alcohol **4a**

Next, in order to explore the scope of the above process, we have also investigated the direct allylation of imidazole **2a** with acyclic MBH alcohol **1**. In our first experiment, this sustrate did not react with imidazole **2a** in toluene at reflux, within 24 h, with or without azeotropic distillation, and the starting materials were completely recovered (Table 2, entry 1). Moreover, the addition of additives to the previous reaction mixture, such as DMAP[16-19] or molecular sieves 4 Å, commonly used to mediate nucleophilic allylic substitutions, did not lead to a notable improvement of the reaction outcome (Table 2, entries 2,3). However the use of DABCO, commonly used as a powerful catalyst or a nucleophilic additive in the

reaction of acyclic MBH adducts with various nucleophiles,[13,22-25] did not afford the S_N2/ S_N2' products but provided the 1,4-adduct **8** in 84% yield (Table 2, entry 4). Alternatively, we also investigated the reaction of alcohol **1** and imidazole **2a** (2 equiv), without any catalyst or additive, in refluxing methanol, commonly employed as solvent in the conversion MBH adducts using a variety of amines.[26] Our study showed that the imidazole **2a** reacted with alcohol **1**, without any additive or in the presence of DABCO, as additive, in a 1,4-fashion, leading to the imidazole derivative **8,** within 10 h, in 65-68 % yields (Table 2, entries 5,6).

Table 2. Optimization of the reaction conditions of imidazole **2a** with acyclic MBH **1**.



1 **2a** **8**

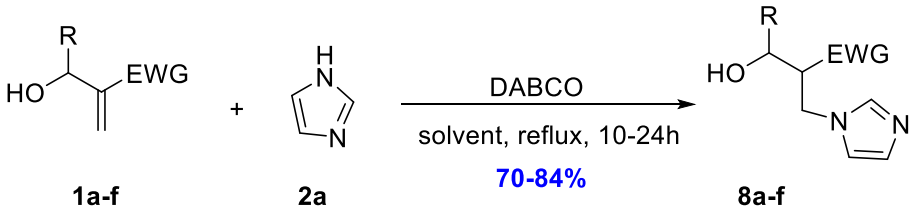
Entry	Additive (1 equiv)	Solvent	Time (h)	**8** (Yield %)
1	None	Toluene	24	n.r
2	MS 4Å	Toluene	24	n.r
3	DMAP	Toluene	24	25
4	DABCO	Toluene	24	84
5	None	MeOH	10	65
6	DABCO	MeOH	10	68

Therefore, in our further experiments on imidazole-mediated the conversion of acyclic MBH alcohols, the toluene at reflux was retained as solvent of choice for the reaction using DABCO as additive.

Next, the treatment of acrylate-derived alcohols **1b,c** (**1b**, EWG=CO_2Et, R=Ph; **1c**, EWG = CO_2Me, R=Me), under the previously optimized conditions, afforded the corresponding 1,4-adducts **8b,c**, in 70-75% yields, (Table 3, entries 2,3), as 55:45 and 59:41 mixtures of inseparable diastereomers, respectively. The relative diastereomeric ratios (dr) were determined by means of ^{1}H NMR based on the proton at the α position of the EWG moiety (Table 3).

In order to explore the scope of this synthetic approach, we have studied the reaction of ketone-derived alcohols such as **1d** (EWG=COPh, R=H), **1e** (EWG=CO^{n}Pr, R=H), **1f** (EWG=COc-C_6H_{11}, R = H), and imidazole under the established reaction conditions, and we have observed that the conversion was complete but wasn't clean. However in methanol at reflux, a clean reaction took place, providing the corresponding 1,4-adducts **8d-f** in 70-76% yields (Table 3, entries 4-6).

Table 3. Michael additions of imidazole **2a** onto acyclic MBH alcohols **1a-f**



R = H, Me, Ph
EWG = CO_2Et, CO_2Me, COPh, CO^nPr, COC_6H_{11}

Entry	Product	R	EWG	Solvent	Time (h)	**8** (Yield %), dr[a]
1	**8a**	H	CO_2Et	Toluene	24	84 None
2	**8b**	Ph	CO_2Et	Toluene	24	75 55:45
3	**8c**	Me	CO_2Me	Toluene	24	70 59:41
4	**8d**	H	COPh	MeOH	10	70 None
5	**8e**	H	CO^nPr	MeOH	12	76 None
6	**8f**	H	COC_6H_{11}	MeOH	12	73 None

[a]Determined from ^{1}H NMR of the crude reaction mixture.

■ CONCLUSIONS

We have successfully developed an efficient *N*-nucleophilic allylic substitutions of cyclic MBH alcohols **4** and acetates **5** with imidazoles in refluxing toluene. The new *N*-substituted imidazoles **6,7** were afforded in high purity and good yields.

In toluene or methanol at reflux, acyclic MBH alcohols reacted with imidazole in a 1,4-fashion, leading to the corresponding Michael adducts **8** in 70-84% yields.

Synthetic applications of such imidazole derivatives,[14,27] as well as their biological evaluation[28] work underway in our laboratory.

■ EXPERIMENTAL SECTION

IR spectra were recorded on a Bruker (IFS 66v/S) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AC-500 spectrometer (300 MHz for 1H and 125 MHz for ^{13}C) in $CDCl_3$, using TMS as an internal standard (chemical shifts in d values, J in Hz). High resolution mass spectra (HRMS) were recorded as EI-HRMS on an Autospec Ultima/micromass mass spectrometer. Gas chromatography–mass spectrometry (GCMS) were recorded on an Agilent Technologies 6890N. Analytical thin layer chromatography (TLC) was performed using Fluka Kieselgel 60 F254 precoated silica gel plates. Visualization was achieved by UV light (254 nm). Flash chromatography was performed using Merck silica gel 60 and a gradient solvent system ether/acetone as eluant).

Typical procedure for the α-substitution of cyclic MBH adducts with imidazoles

A mixture of allyl acetate **5a** (2 mmol, 0.33 g) or allyl alcohol **4a** (2 mmol, 0.25 g) and imidazole **2a** (4 mmol, 0.27 g) in toluene (25 mL) was heated under reflux (for **5a**) or in a Dean stark apparatus (for **4a**). After completion (TLC), the reaction mixture was cooled, washed with brine and dried. The toluene was removed and the residue was purified by column chromatography on silica gel (acetone/ether, 8:2) to give the pure *N*-substituted imidazole **6a**.

2-((1H-imidazol-1-yl)methyl)cyclohex-2-enone 6a

Yield: 82%; yellow oil; ν ($CHCl_3$) 2932, 1666, 1503, 1380, 1227, 1074 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.47 (s, 1H), 7.01 (s, 1H), 6.89 (s, 1H), 6.64 (t, J = 4.0 Hz, 1H), 4.70 (s, 2H), 2.47–2.35 (m, 4H), 2.04–1.98 (m, 2H); ^{13}C NMR ($CDCl_3$,

125 MHz): δ_C 197.6, 147.7, 137.6, 135.2, 129.3, 119.4, 45.5, 37.9, 25.8, 22.6; HRMS (EI): MH^+, found 177.1022. $C_{10}H_{13}N_2O$ requires 177.1028.

2-((1H-imidazol-1-yl)methyl)cyclopent-2-enone 6b

Yield: 65%; yellow oil; ν ($CHCl_3$) 2924, 1693, 1504, 1388, 1227, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H 7.51 (s, 1H), 7.34 (t, *J* = 4.0 Hz, 1H), 7.02 (s, 1H), 6.94 (s, 1H), 4.71 (s, 2H), 2.64–2.60 (m, 2H), 2.46–2.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 207.2, 160.2, 142.1, 137.4, 129.5, 119.3, 41.7, 34.6, 26.7; HRMS (EI): MH^+, found 163.0866. $C_9H_{11}N_2O$ requires 163.0871.

2-((1H-imidazol-1-yl)ethyl)cyclohex-2-enone 6c

Yield: 75%; yellow oil; ν ($CHCl_3$) 2935, 1665, 1497, 1381, 1226, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H 7.55 (s, 1H), 7.03 (s, 1H), 6.93 (s, 1H), 6.57 (t, *J* = 4.0 Hz, 1H), 5.34 (q, *J* = 6.2 Hz, 1H), 2.47–2.36 (m, 4H), 2.02–1.96 (m, 2H), 1.62 (d, *J* = 6.2 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 197.3, 145.4, 140.4, 136.2, 128.9, 117.8, 50.4, 38.4, 25.7, 22.4, 19.8; MS (m/z): 191 (13), 190 (M+, 100), 189 (8), 175 (15), 162 (16), 149 (7), 134 (7), 123 (62), 107 (10), 95 (48), 81 (27), 79 (38), 69 (50), 67 (75), 55 (50); HRMS (EI): MH^+, found 191.1188. $C_{11}H_{15}N_2O$ requires 191.1184.

2-((1H-imidazol-1-yl)ethyl)cyclopent-2-enone 6d

Yield: 69%; yellow oil; ν ($CHCl_3$) 2926, 1695, 1496, 1395, 1227, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H 7.59 (s, 1H), 7.28 (t, *J* = 4.0 Hz, 1H), 7.03 (s, 1H), 7.01 (s, 1H), 5.11 (q, *J* = 6.0 Hz, 1H), 2.62–2.60 (m, 2H), 2.46–2.43 (m, 2H), 1.71 (d, *J* = 6.0 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 207.2, 159.1, 146.6, 136.0, 129.0, 117.8, 49.1, 35.2, 26.6, 19.5; MS (m/z): 177 (12), 176 (M+, 100), 175 (7), 161 (1), 147 (9), 109 (43), 81 (54), 79 (74), 69 (33), 67 (13), 53 (31); HRMS (EI): MH^+, found 177.1031. $C_{10}H_{13}N_2O$ requires 177.1028.

2-((1H-benzimidazol-1-yl)ethyl)cyclohex-2-enone 7a

Yield: 87%; yellow oil; ^1H NMR ($CDCl_3$, 500 MHz): δ_H 8.03 (s, 1H), 7.73–7.71 (m, 1H), 7.21–7.15 (m, 3H), 6.49 (t, *J* = 4.0 Hz, 1H), 5.52 (q, *J* = 6.0 Hz, 1H), 2.38–2.34 (m, 2H), 2.25–2.19 (m, 2H), 1.89–1.83 (m, 2H), 1.70 (d, *J* = 6.0 Hz,

3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 197.5, 146.0, 143.7, 141.3, 133.9, 133.2, 122.8, 122.1, 120.1, 110.4, 49.1, 38.1, 25.6, 22.3, 19.4 ; MS (m/z): 241 (17), 240 (M+, 100), 239 (10), 226 (15), 225 (100), 211 (10), 197 (7), 183 (5), 169 (5), 145 (14), 119 (15), 118 (55), 91 (8), 77 (7), 67 (9), 55 (5); HRMS (EI): MH^+, found 241.1347. $C_{15}H_{17}N_2O$ requires 241.1341.

2-((1H-benzimidazol-1-yl)methyl)cyclohex-2-enone 7b

Yield: 80%; yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.85 (s, 1H), 7.68–7.62 (m, 1H), 7.22–7.08 (m, 3H), 6.49 (t, *J* = 4.0 Hz, 1H), 4.78 (s, 2H), 2.30–2.25 (m, 2H), 2.15–2.10 (m, 2H), 1.82–1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 197.7, 147.8, 143.6, 143.3, 133.8, 133.3, 122.6, 121.7, 119.9, 109.6, 43.2, 37.6, 25.3, 22.2; MS (m/z): 227 (16), 226 (M+, 100), 225 (33), 211 (5), 198 (28), 197 (19), 183 (7), 170 (30), 169 (24), 157 (7), 131 (22), 118 (15), 104 (4), 90 (5), 77 (7), 63 (3), 53 (6); HRMS (EI): MH^+, found 227.1189. $C_{14}H_{15}N_2O$ requires 227.1184.

2-((1H-benzimidazol-1-yl)methyl)cyclopent-2-enone 7c

Yield: 72%; yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.92 (s, 1H), 7.75–7.74 (m, 1H), 7.29–7.18 (m, 4H), 4.87 (s, 2H), 2.51–2.49 (m, 2H), 2.39–2.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 207.6, 160.6, 143.6, 143.4, 140.9, 133.4, 123.1, 122.2, 120.3, 109.6, 39.7, 34.5, 26.7; MS (m/z): 213 (14), 212 (M+, 100), 211 (46), 197 (2), 184 (11), 183 (39), 169 (17), 156 (21), 131 (10), 118 (14), 104 (5), 90 (4), 77 (5), 63 (3), 53 (3); HRMS (EI): MH^+, found 213.1033. $C_{13}H_{13}N_2O$ requires 213.1028.

2-((1H-benzimidazol-1-yl)ethyl)cyclopent-2-enone 7d

Yield: 85%; yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 8.01 (s, 1H), 7.72–7.69 (m, 1H), 7.25–7.12 (m, 4H), 5.25 (q, *J* = 6.0 Hz, 1H), 2.46–2.42 (m, 2H), 2.31–2.30 (m, 2H), 1.74 (d, *J* = 6.0 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 207.1, 159.3, 145.1, 143.4, 141.1, 132.9, 122.7, 122.1, 120.02, 110.2, 47.4, 34.8, 26.2, 18.6; MS (m/z): 227 (16), 226 (M+, 100), 225 (8), 211 (38), 197 (14), 183 (13), 169

(4), 156 (1), 119 (12), 118 (74), 109 (8), 91 (9), 79 (14),77 (7), 63 (5), 53 (7); HRMS (EI): MH^+, found 227.1190. $C_{14}H_{15}N_2O$ requires 227.1184.

Typical procedure for the preparation of imidazole derivatives 8

A mixture of acyclic MBH alcohol **1** (1 mmol), imidazole **2a** (2 mmol) and DABCO (1 mmol), was stirred at reflux of methanol or toluene. After completion of the reaction, the solvent was removed by a rotary evaporation and CH_2Cl_2 (10 mL) was added. The reaction mixture was washed with brine and dried. Finally, the solvent was removed and the residue was purified by a column chromatography on silica gel, using acetone/ether as eluent, to give the pure imidazole derivative **8**.

Ethyl 2-((1H-imidazol-1-yl)methyl)-3-hydroxypropanoate 8a

Yield: 84%; yellow oil; ν ($CHCl_3$) 3118, 2982, 2934, 1723, 1509, 1451, 1376, 1282, 1225, 1181, 1071 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.52 (s, 1H), 6.99 (s, 1H), 6.95 (s, 1H), 4.77 (s, 1H, O<u>H</u>), 4.35 (d, *J* = 6.6 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.81–3.73 (m, 2H), 2.97–2.91 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 171.8, 137.8, 128.7, 119.6, 61.2, 59.3, 49.2, 44.6, 14.0; HRMS (EI): MH^+, found 199.1085. $C_9H_{15}N_2O_3$ requires 199.1083.

Ethyl 2-((1H-imidazol-1-yl)methyl)-3-hydroxy-3-phenylpropanoate 8b

Overall yield: 75%; yellow oil; dr = 55:45. Major diastereomer ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.41–7.22 (m, 6H), 6.83–6.76 (m, 2H), 4.85 (d, *J* = 6.7 Hz, 1H), 4.46–3.81 (m, 4H), 3.19–3.12 (m, 1H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 172.0, 141.1, 137.3, 129.0, 128.2, 128.2, 126.1, 119.1, 72.6, 61.2, 55.0, 45.6, 13.9. Minor diastereomer ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.41–7.22 (m, 6H), 6.83–6.76 (m, 2H), 4.92 (d, *J* = 7.3 Hz, 1H), 4.46–3.81 (m, 4H), 3.07–3.01 (m, 1H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 171.8, 141.7, 137.4, 129.0, 128.4, 128.0, 126.3, 119.3, 72.6, 61.., 55.8, 45.3, 13.7; HRMS (EI): MH^+, found 275.1402. $C_{15}H_{19}N_2O_3$ requires 275.1396.

Methyl 2-((1H-imidazol-1-yl)methyl)-3-hydroxybutanoate 8c

Overall yield: 70%; yellow oil; dr = 59:41. Major diastereomer ^1H NMR ($CDCl_3$, 300 MHz): δ_H δ_H 7.46 (s, 1H), 6.98 (s, 1H), 6.89 (s, 1H), 5.17 (s, 1H, O<u>H</u>), 4.43–

4.30 (m, 2H), 4.05–3.99 (m, 1H), 3.62 (s, 3H), 2.84–2.77 (m, 1H), 1.27 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 172.8, 137.4, 128.8, 119.4, 66.1, 55.5, 52.0, 45.9, 21.9. Minor diastereomer ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.49 (s, 1H), 6.99 (s, 1H), 6.93 (s, 1H), 5.17 (s, 1H, OH), 4.43–4.30 (m, 2H), 4.05–3.99 (m, 1H), 3.67 (s, 3H), 2.92–2.87 (m, 1H), 1.25 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 172.3, 137.5, 128.9, 119.4, 65.8, 54.3, 52.0, 45.0, 20.7; HRMS (EI): MH^+, found 199.1085. $C_9H_{15}N_2O_3$ requires 199.1083.

3-Hydroxy-2-((1H-imidazol-1-yl)methyl)-1-phenylpropan-1-one 8d

Yield: 70%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.85–7.82 (m, 2H), 7.56–7.36 (m, 4H), 6.90 (s, 1H), 6.87 (s, 1H), 6.41 (s, 1H, OH), 4.52–4.34 (m, 2H), 4.02–3.94 (m, 1H), 3.88–3.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 199.8, 137.6, 136.1, 133.6, 128.8, 128.7, 128.2, 119.7, 60.7, 51.5, 45.1; HRMS (EI): MH^+, found 231.1132. $C_{13}H_{15}N_2O_2$ requires 231.1134.

1-Hydroxy-2-((1H-imidazol-1-yl)methyl)hexan-3-one 8e

Yield: 76%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.45 (s, 1H), 6.97 (s, 1H), 6.89 (s, 1H), 4.63 (s, 1H, OH), 4.36–4.17 (m, 2H), 3.80–3.69 (m, 2H), 3.11–3.05 (m, 1H), 2.56–2.26 (m, 2H), 1.56–1.49 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 210.6, 137.7, 128.9, 119.5, 59.8, 55.7, 44.9, 44.5, 16.7, 13.5; HRMS (EI): MH^+, found 197.1293. $C_{10}H_{17}N_2O_2$ requires 197.1290.

1-Cyclohexyl-3-hydroxy-2-((1H-imidazol-1-yl)methyl)propan-1-one 8f

Yield: 73%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.43 (s, 1H), 6.96 (s, 1H), 6.88 (s, 1H), 4.71 (s, 1H, OH), 4.36–4.16 (m, 2H), 3.74–3.41 (m, 2H), 3.31–3.24 (m, 1H), 2.42–2.34 (m, 1H), 1.72–1.54 (m, 5H), 1.43–1.15 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 213.6, 137.6, 128.8, 119.5, 60.3, 54.4, 50.8, 45.0, 29.6, 28.0, 27.2, 25.7, 25.2; HRMS (EI): MH^+, found 237.1607. $C_{13}H_{21}N_2O_2$ requires 237.1603.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at

^{1}H and ^{13}C NMR and HRMS spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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