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Synthesis of β-hydroxyacetamides from unactivated ethyl acetates under base-free conditions and microwave irradiation

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ABSTRACT

The amidation of unactivated ethyl esters with achiral and chiral 1,2-amino alcohols under microwave irradiation and base-free conditions is described. This procedure provides a convenient method for the synthesis of β-hydroxyacetamides bearing pyrazole, imidazole, and benzimidazole groups in high yields and without racemization. The protocol described herein is environmentally friendly and allows for the preparation of a wide variety of β-hydroxyacetamides, which are key intermediates in the synthesis of oxazolines and other derivatives of biological interest.

1. Introduction

Amide bond formation is a general and versatile reaction widely used to prepare peptides, polymers, and other complex molecules. The mildest conditions require activation of the carboxylic acid derivatives using stoichiometric quantities of activating or condensing agents.[1] Amides bearing chiral 1,2-amino alcohols, which have been used as building blocks in the synthesis of more complex molecules,[2] and as chiral ligands,[3] are usually prepared by the reaction of activated carboxylic acids with chiral 1,2-amino alcohols. Other amides bearing chiral amino alcohols have been obtained by reactions between mildly activated esters and 1,2-amino alcohols without the need of coupling reagents,[4] or in a single-step carbene-catalyzed reaction of esters with chiral 1,2-amino alcohols,[5] catalyzed by 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP),[6] and using K_3PO_4 as the catalyst.[7] However, these methods suffer from one or more disadvantages such as the use of specialized handling techniques and tedious work-up, long reaction times, vigorous reaction conditions, the requirement of an excess of reagents, the use of solvent, which leads to unsatisfactory yields, and a lack of generality.

On the other hand, Microwave-Assisted Organic Synthesis (MAOS) has been successfully applied in the synthesis of amide from non-activated acids, and optically active compounds are compatible with these methods.[8] However, the preparation of amides bearing chiral 1,2-amino alcohols under microwave irradiation has not been reported. Therefore, in connection with our previous studies concerning the synthesis of amides bearing chiral 1,2-amino alcohols,[9] we herein report an operationally simple, and expeditious base-free synthesis of several β-hydroxyamides from unactivated esters under microwave irradiation. The versatility of this method was exploited to obtain β-hydroxyamides, with moderate to excellent yields in very short reaction times, which can be used as key intermediates in the synthesis of more complex molecules and as ligands.

2. Results and discussion

For the synthesis of target compound **1**, we envisaged two synthetic procedures: (a) reaction of easily obtained *N*-chloroacetamido alcohols **2**, with several cyclic amines, and (b) the reaction of ethyl acetate derivative **3** with chiral 1,2-amino alcohols (Scheme 1).

Initially we developed a general procedure to prepare the novel β-hydroxyacetamides **1a**–**f** following route A. In this context, using a recently described procedure the *N*-chloroacetamido alcohol **2** was readily obtained,[9,10] which was then reacted with different heterocyclic amines such as pyrrolidine, piperidine, and morpholine in the presence of K_2CO_3 in CH_3CN at room temperature, obtaining the

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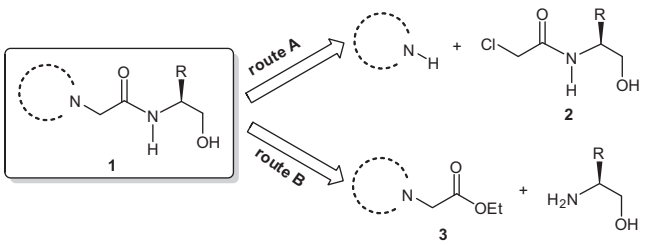
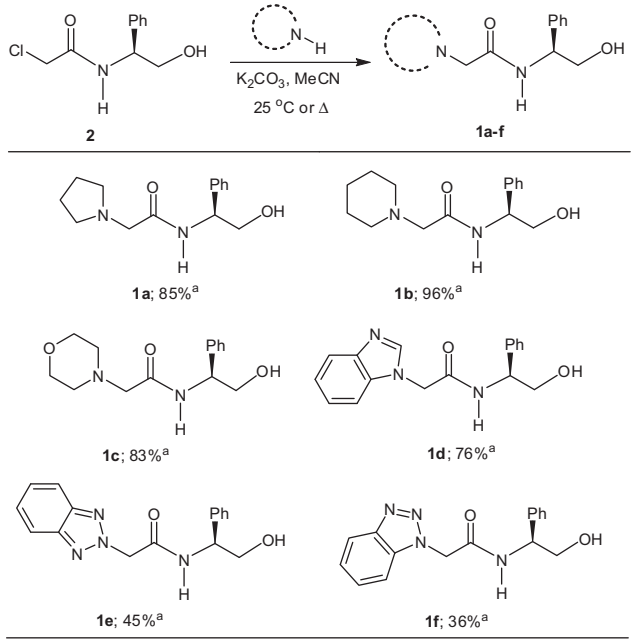


Scheme 1. Retrosynthetic analysis of **1**.

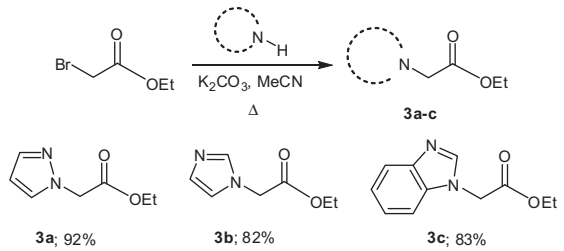
target compounds **1a–c** in good yields (83–96%). Under identical conditions, the reaction of *N*-chloroacetamido alcohol **2** with benzimidazole afforded β-hydroxyacetamide **1d** in 76% yield, whereas the reaction of **2** with benzotriazole gave a mixture of two regioisomers **1e** and **1f** in 45% and 36% yields, respectively (Table 1).

Table 1
Reaction of **2** with several cyclic amines



[a] Isolated after purification by column chromatography.

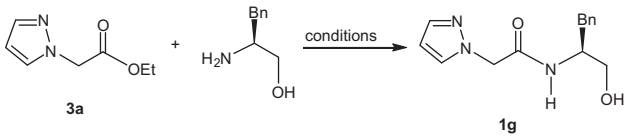
On the other hand, route B started with the nucleophilic substitution reaction of ethyl bromoacetate with pyrazole, imidazole, and benzimidazole in the presence of K_2CO_3 in CH_3CN at reflux for 3 h, to give compounds **3a–c** in 82–92% yield (Scheme 2).



Scheme 2. Preparation of **3a–c**.

After the preparation of acetate derivatives **3a–c**, the next step was to explore the scope of the substitution reaction with several 1,2-amino alcohols in order to obtain the target compounds. In this context, we carried out the reaction of **3a** with (*S*)-phenylalaninol in ethanol at 70 °C for 8 h, to obtain the desired compound **1g** in 22% yield (Table 2, entry 1). We suspected that the poor yield could be strongly influenced by the temperature at which the reaction took place; therefore we decided to change the solvent and carry out the reaction in toluene at reflux for 8 h, and obtained the desired product **1g** in 50% yield (Table 2, entry 2). On the other hand, it is well known that microwave irradiation is able to speed up certain chemical reactions and increase the yield. With this in mind, we carried out the reaction of **3a** with (*S*)-phenylalaninol in toluene at 120 °C for 25 min under microwave irradiation, and obtained compound **1g** in 89% yield (Table 2, entry 3). Compound **1g** was obtained in 94% yield when the reaction was conducted at 180 °C for 10 min (Table 2, entry 4).

Table 2
Preparation of pyrazolyl-hydroxyacetamide **1g**



Entry	Conditions	Yield[a] (%)
1	EtOH, 70 °C, 8 h	22
2	PhMe, 110 °C, 8 h	50
3	MW, PhMe, 120 °C, 25 min	89
4	MW, PhMe, 180 °C, 10 min	94

[a] Isolated after purification by column chromatography.

Having identified the optimal reaction conditions, we next investigated the generality of the reaction of **3a–c** with several 1,2-amino alcohols. Our results show that the reaction of **3a–c** with (*S*)-phenylalaninol afforded β-hydroxyacetamides (*S*)-**1g–i** in excellent yields (91–96%). In a similar manner, the reaction of **3a–c** with (*R*)-phenylglycinol produced the corresponding β-hydroxyacetamides (*R*)-**1j–l** in 83–96% yield. On the other hand, when **3a–c** was reacted with ethanolamine, the achiral β-hydroxyacetamides **3m–o** were obtained in excellent yield. Treatment of **3a–c** with (*S*)-alalinol under microwave irradiation gave the β-hydroxyacetamides (*S*)-**1p–r** in 52–84% yield. Finally, the reaction of **3a–c** with (*S*)-valinol produced the β-hydroxyacetamides (*S*)-**1s–u** in good to excellent yields (Table 3).

3. Conclusion

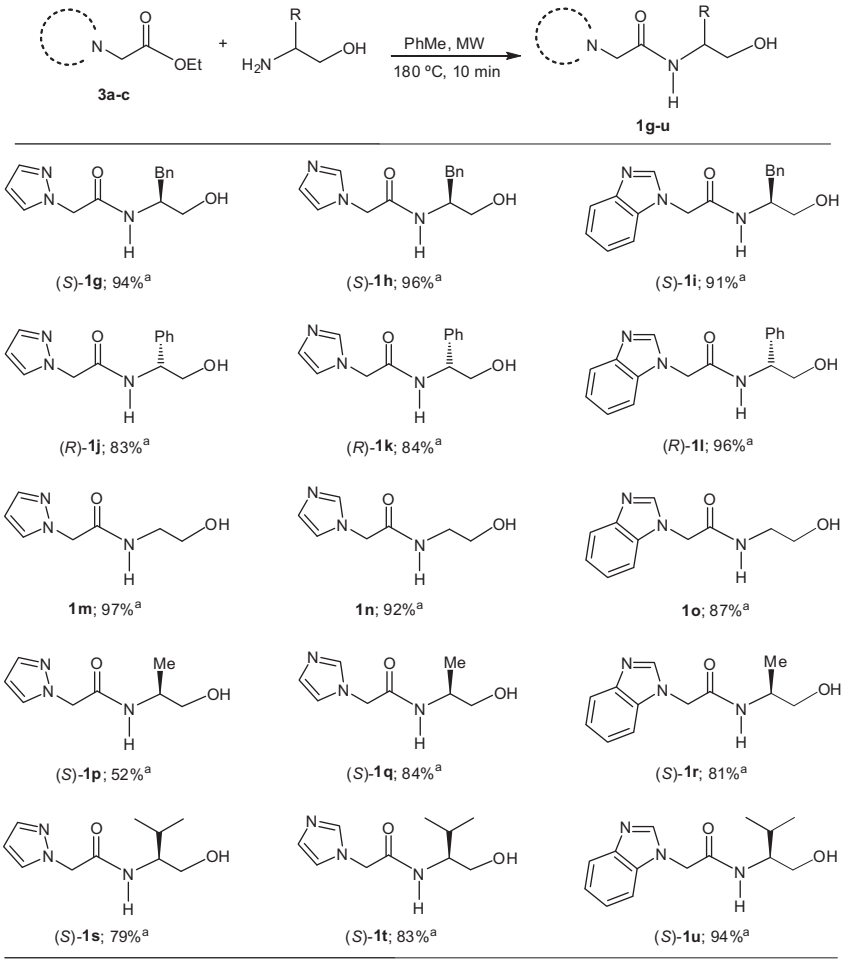
In conclusion, we have developed a rapid, practical, and efficient method for the synthesis of a variety of amides bearing achiral and chiral 1,2-amino alcohols and pyrazole, imidazole, and benzimidazole, under microwave irradiation. These compounds have great potential as key intermediates in the synthesis of important bioactive compounds or as chiral ligands in asymmetric catalysts. Studies on the biological activity of these compounds are currently in progress.

4. Experimental

4.1. General

All commercial materials were used as received unless noted otherwise. Melting points were registered using a Mel-Temp II apparatus and are uncorrected. Flash chromatography was performed using 230–400 mesh Silica Flash 60® silica gel. Thin layer

Table 3
Synthesis of β-hydroxyacetamides **1g–u** under microwave irradiation



[a] Isolated after purification by column chromatography.

chromatography was carried out on pre-coated TLC sheets of silica gel 60 F254 (E. Merck). NMR spectra were recorded on Varian System instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C. The spectra were obtained in $CDCl_3$, CD_3OD, and DMSO-d_6 solution using TMS as the internal reference. Chemical shifts (δ) are reported in parts per million. Multiplicities are recorded as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, bs = broad singlet, q = quartet and m = multiplet. Coupling constants (J) are given in Hz. High resolution CI$^+$ and FAB$^+$ mass experiments were carried out in a JEOL HRMStation JHRMS-700. Optical rotations were measured with an Anton-Paar MCP 300 polarimeter in a 2.5 mm cell. Reactions carried out with stirring under microwave irradiation in the closed-vessel were all performed with a Microwave Synthesis Reactor (Monowave 300/ Anton Paar).

4.2. General procedure for the synthesis of compounds 1a–c

To a suspension of (*S*)-2-chloro-*N*-(2-hydroxy-1-phenylethyl) acetamide **2**[10] (1.0 equiv) and K_2CO_3 (1.2 equiv) in acetonitrile (4 mL) at 0 °C, the corresponding amine (1.0 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and then stirred overnight or heated at reflux. The solvent was evaporated under reduced pressure, and water (10 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The solid obtained was purified by flash chromatography on silica gel using EtOAc as eluent or by crystallization in hot EtOAc for **1a–c** or by flash column chromatography using EtOAc/Hex/MeOH (5:4:1) as eluent for **1d–f**.

4.2.1. (*S*)-*N*-(2-Hydroxy-1-phenylethyl)-2-(pyrrolidin-1-yl)acetamide 1a

(211 mg, 85%) as a white solid, mp 114 °C, $[\alpha]_D$ = +30.7 (*c* 3.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74–1.83 (m, 4H), 2.57–2.66 (m, 5H), 3.19 (AB system, J = 16.4 Hz, 2H, CH_2C=O), 3.85–3.88 (m, 2H, CH_2OH), 5.05–5.09 (m, 1H, CHPh), 7.27–7.31 (m, 3H, H_{arom}), 7.35–7.39 (m, 2H, H_{arom}), 7.8 (d, J = 6.7 Hz, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 54.7, 56.0, 59.5, 66.9 (CH_2OH), 126.8, 128.0, 129.0, 139.2, 171.9 (C=O). HRMS (FAB$^+$): calculated for $C_{14}H_{21}N_2O_2$ [M+H]$^+$, m/z 249.1603; found for [M+H]$^+$, m/z 249.1607.

4.2.2. (*S*)-*N*-(2-Hydroxy-1-phenylethyl)-2-(piperidin-1-yl)acetamide 1b

(252 mg, 96%) as a light yellow oil, $[\alpha]_D$ = +28.0 (*c* 3.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (bs, 2H), 1.55–1.59 (m, 4H), 2.47 (m, 5H), 3.01 (AB system, J = 16.4 Hz, 2H, CH_2C=O), 3.87 (d, J = 5.2 Hz, 2H, CH_2OH), 5.04–5.09 (m, 1H, CHPh), 7.27–7.40 (m, 5H, H_{arom}), 8.01 (bs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 26.1, 54.9, 56.0, 62.2, 67.2 (CH_2OH), 126.5, 127.9, 128.9, 138.9, 171.7 (C=O). HRMS (FAB$^+$): calculated for $C_{15}H_{23}N_2O_2$ [M+H]$^+$, m/z 263.1760; found for [M+H]$^+$, m/z 263.1752.

4.2.3. (*S*)-*N*-(2-Hydroxy-1-phenylethyl)-2-morpholin-acetamide 1c

(220 mg, 83%) as a colorless oil, $[\alpha]_D$ = +36.0 (*c* 3.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.48–2.60 (m, 5H), 3.05 (AB system, *J* = 16.3 Hz, 2H, $CH_2C{=}O$), 3.7 (t, *J* = 4.6 Hz, 4H), 3.82 (dd, *J* = 11.6, 6.4 Hz, 1H, CH_2OH), 3.86 (dd, *J* = 11.2, 4.4 Hz, 1H, CH_2OH), 5.05–5.09 (m, 1H, CHPh), 7.27–7.32 (m, 3H, H_{arom}), 7.35–7.39 (m, 2H, H_{arom}), 7.83 (d, *J* = 7.4 Hz, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.9, 55.6, 62.0, 66.7 (CH_2OH), 67.1, 126.7, 128.1, 129.0, 139.1, 170.6 (C=O). HRMS (FAB^+): calculated for $C_{14}H_{21}N_2O_3$ $[M+H]^+$, *m*/*z* 265.1552; found for $[M+H]^+$, *m*/*z* 265.1547.

4.2.4. (*S*)-*N*-(2-Hydroxy-1-phenylethyl)-2-(1*H*-benzo[*d*]-imidazol-1-yl)acetamide 1d

(215 mg, 76%) as a white solid, mp 217–219 °C, $[\alpha]_D$ = +86.8 (*c* 3.0, DMSO). ^1H and ^{13}C NMR data are identical to those described in the literature[11] HRMS (FAB^+): calculated for $C_{17}H_{18}N_3O_2$ $[M+H]^+$, *m*/*z* 296.1399; found for $[M+H]^+$, *m*/*z* 296.1413.

4.2.5. (*S*)-*N*-(2-Hydroxy-1-phenylethyl)-2-(2*H*-benzo[*d*]-[1,2,3] triazol-2-yl)acetamide 1e

(125 mg, 45%) as a white solid, mp 202–203 °C, $[\alpha]_D$ = +128.0 (*c* 3.0, DMSO). ^1H NMR (400 MHz, DMSO-d_6): δ = 3.58–3.68 (m, 2H, CH_2OH), 4.83–4.91 (m, 1H, CHPh), 5.05 (t, *J* = 5.6 Hz, 1H, OH), 5.58 (s, 2H, $CH_2C{=}O$), 7.23–7.29 (m, 1H, H_{arom}), 7.31–7.38 (m, 4H, H_{arom}), 7.43 (dd, *J* = 6.4, 3.2 Hz, 2H, H_{arom}), 7.91 (dd, *J* = 6.6, 3.0 Hz, 2H, H_{arom}), 8.94 (d, *J* = 8.4 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.5 ($CH_2C{=}O$), 58.4 (CHPh), 64.6 (CH_2OH), 117.9, 126.6, 127.0, 127.1, 128.3, 140.6, 144.0, 164.7 (C=O). HRMS (FAB^+): calculated for $C_{16}H_{17}N_4O_2$ $[M+H]^+$, *m*/*z* 297.1352; found for $[M+H]^+$, *m*/*z* 297.1344.

4.2.6. (*S*)-*N*-(2-Hydroxy-1-phenylethyl)-2-(1*H*-benzo[*d*]-[1,2,3] triazol-1-yl)acetamide 1f

(101 mg, 36%) as a white solid, mp 233–234 °C, $[\alpha]_D$ = +130.65 (*c* 3.0, DMSO). ^1H NMR (400 MHz, DMSO-d_6): δ = 3.59–3.68 (m, 2H, CH_2OH), 4.85–4.90 (m, 1H, CHPh), 5.07 (t, *J* = 5.4 Hz, 1H, OH), 5.56 (s, 2H, $CH_2C{=}O$), 7.23–7.27 (m, 1H, H_{arom}), 7.31–7.35 (m, 4H, H_{arom}), 7.37–7.41 (m, 1H, H_{arom}), 7.52 (ddd, *J* = 8.4, 6.8, 0.8 Hz, 1H, H_{arom}), 7.74–7.77 (m, 1H, H_{arom}), 8.02–8.04 (m, 1H, H_{arom}), 9.02 (d, *J* = 8.4 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.4 ($CH_2C{=}O$), 55.9 (CHPh), 65.0 (CH_2OH), 111.4, 119.4, 124.3, 127.3, 127.4, 127.7, 128.6, 134.1, 141.0, 145.5, 165.7 (C=O). HRMS (FAB^+): calculated for $C_{16}H_{17}N_4O_2$ $[M+H]^+$, *m*/*z* 297.1352; found for $[M+H]^+$, *m*/*z* 297.1344.

4.3. General procedure for the synthesis of compounds 3a–c

A solution of the corresponding azole (imidazole, pyrazole, and benzimidazole) (1.0 equiv) in CH_3CN (30 mL) was treated with K_2CO_3 (2.1 equiv) and ethyl bromoacetate (1.0 equiv). The reaction mixture was stirred at reflux for 3 h, after which the reaction mixture was quenched by the addition of a saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography using hexane-ethyl acetate (7:3) for derivatives bearing a pyrazole and imidazole, or ethyl acetate/hexane/methanol (5:4:1) for the benzimidazole derivative.

4.3.1. Ethyl 2-(1*H*-pyrazol-1-yl)acetate 3a

(1.70 g, 92%) as a light yellow oil, ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3H, CH_3CH_2O), 4.23 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.92 (s, 2H, $CH_2C{=}O$), 6.33 (dd, *J* = 2.2, 2.1 Hz, 1H, CH=CH—N), 7.48 (d, *J* = 2.3 Hz, 1H, CH=N), 7.56 (d, *J* = 1.8 Hz, 1H, CH—N). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3CH_2), 53.1 ($CH_2C{=}O$), 61.8 (CH_2O), 106.5 (CH=CH—N), 130.6 (CH—N), 140.1 (CH=N), 168.0 (C=O). HRMS (CI^+): calculated for $C_7H_{11}N_2O_2$ $[M+H]^+$, *m*/*z* 155.0821; found for $[M+H]^+$, *m*/*z* 155.0815.

4.3.2. Ethyl 2-(1*H*-imidazol-1-yl)acetate 3b

(1.56 g, 82%) as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3H, CH_3CH_2O), 4.24 (q, *J* = 7.2 Hz, 2H, O**C**H_2CH_3), 4.70 (s 2H, $CH_2C{=}O$), 6.96 (s, 1H, NCH=CH), 7.09 (s, 1H, NCH=CH), 7.50 (s, 1H, N=CH**N**). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (**C**H_3), 48.0 ($CH_2C{=}O$), 62.0 (OCH_2CH_3), 120.0, 129.6, 137.9, 167.4 (**C**=**O**). HRMS (FAB^+): calculated for $C_7H_{11}N_2O_2$ $[M+H]^+$, *m*/*z* 155.0821; found for $[M+H]^+$, *m*/*z* 155.0822.

4.3.3. Ethyl 2-(1*H*-benzo[d]imidazol-1-yl)acetate 3c

(2.81 g, 83%) as a white solid, mp 63–64 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O), 4.20 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.83 (s, 2H, $CH_2C{=}O$), 7.26–7.33 (m, 3H, H_{arom}), 7.78–7.83 (m, 1H, H_{arom}), 7.88 (s, 1H, N=CH—N). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3CH_2O), 46.1 ($CH_2C{=}O$), 62.2 (OCH_2CH_3), 109.3, 120.5, 122.5, 123.4, 143.5, 167.3 (C=O). HRMS (FAB^+): calculated for $C_{11}H_{13}N_2O_2$ $[M+H]^+$, *m*/*z* 205.0977; found for $[M+H]^+$, *m*/*z* 205.0977.

4.4. General procedure for the synthesis of compounds 1g–u

In a capped 10 mL MW-vessel, the ethyl azolyl-acetate derivatives **3a–c** (1.0 equiv), the corresponding 1,2-amino alcohol (1.0 equiv) and toluene (3 mL) were mixed. The tube was positioned in the irradiation cavity and the mixture was heated with stirring under microwave irradiation at 180 °C and held for approximately 10 min. The vessel was cooled to room temperature, and the residue was dissolved in methanol and then concentrated under vacuum. The crude product was purified either by flash chromatography on silica gel using EtOAc/Hex/MeOH (5:4:1) as eluent or by crystallization under ethyl acetate. The purity of the final products was determined by ^1H NMR spectroscopy.

4.4.1. (*S*)-*N*-(1-Hydroxy-3-phenylpropan-2-yl)-2-(1*H*-pyrazol-1-yl)acetamide 1g

(318 mg, 94%) as a white solid, mp 113–114 °C. $[\alpha]_D$ = −24.0 (*c* 1.0, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 2.73 (dd, *J* = 13.6, 8.4 Hz, 1H, CH_2Ph), 2.89 (dd, *J* = 13.6, 6.4 Hz, 1H, CH_2Ph), 3.49 (dd, *J* = 11.2, 5.6 Hz, 1H, CH_2OH), 3.54 (dd, *J* = 11.2, 4.8 Hz, 1H, CH_2OH), 4.11 (m, 1H, CHBn), 4.79 (AB system, *J* = 13.6 Hz, 2H, $CH_2C{=}O$), 6.31 (m, 1H, CH—CH=N), 7.18–7.27 (m, 5H, H_{arom}), 7.52 (d, *J* = 1.2 Hz, 1H, CH=N), 7.56 (d, *J* = 2.4 Hz, 1H, CH—N). ^{13}C NMR (100 MHz, CD_3OD): δ = 38.0 (CH_2Ph), 54.60 (CHBn), 55.1 ($CH_2C{=}O$), 63.9 (CH_2OH), 107.2, 127.6, 129. 6 (2C), 130.5 (2C), 133.1, 139.7, 141.2, 169.2 (C=O). HRMS (FAB^+): calculated for $C_{14}H_{18}N_3O_2$ $[M+H]^+$, *m*/*z* 260.1399; found for $[M+H]^+$, *m*/*z* 260.1398.

4.4.2. (*S*)-*N*-(1-Hydroxy-3-phenylpropan-2-yl)-2-(1*H*-imidazol-1-yl)acetamide 1h

(131 mg, 96%) as a white solid, mp 189–190 °C. $[\alpha]_D$ = −10.0 (*c* 1.0, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 2.72 (dd, *J* = 13.6, 8.4 Hz, 1H, CH_2Ph), 2.92 (dd, *J* = 14.0, 6.0 Hz, 1H, CH_2Ph), 3.52 (dd, *J* = 10.8, 5.6 Hz, 1H, CH_2OH), 3.58 (dd, *J* = 10.8, 4.8 Hz, 1H, CH_2OH), 4.14 (m, 1H, CHBn), 4.63 (AB system, *J* = 16.0 Hz, 2H, $CH_2C{=}O$), 6.94 (bs, 2H, CH=CH—N), 7.19–7.28 (m, 5H, H_{arom}), 7.53 (s, 1H, N=CH—N). ^{13}C NMR (100 MHz, CD_3OD): δ = 38.0 (CH_2Ph), 50.3 ($CH_2C{=}O$), 54.5 (CHBn), 64.0 (CH_2OH), 121.6, 127.5 (2C), 128.9, 129.5 (2C), 130.3 (2C), 139.6, 168.9 (C=O). HRMS (FAB^+):

calculated for $C_{14}H_{18}N_3O_2$ $[M+H]^+$, *m*/*z* 260.1399; found for $[M+H]^+$, *m*/*z* 260.1398.

4.4.3. (*S*)-*N*-(1-Hydroxy-3-phenylpropan-2-yl)-2-(1*H*-benzo[*d*]imidazol-1-yl)acetamide 1i

(206 mg, 91%) as a white solid, mp 222–224 °C. $[\alpha]_D = -12.0$ (*c* 1.0, MeOH). ^1H and ^{13}C NMR data are identical to those described in the literature.[11] HRMS (FAB^+): calculated for $C_{18}H_{20}N_3O_2$ $[M+H]^+$, *m*/*z* 310.1556; found for $[M+H]^+$, *m*/*z* 310.1544.

4.4.4. (*R*)-*N*-(2-Hydroxy-1-phenylethyl)-2-(1*H*-pyrazol-1-yl)acetamide 1j

(312 mg, 83%) as a white solid, mp 146–147 °C. $[\alpha]_D = -96.0$ (*c* 1.0, MeOH). ^1H NMR (400 MHz, DMSO-d_6): δ = 3.38 (bs, 1H, OH), 3.59 (br, 2H, CH_2OH), 4.88 (s, 2H, $CH_2C{=}O$), 4.98 (m, 1H, CHPh), 6.24 (t, *J* = 2.0 Hz, 1H, CH=CH—N), 7.22–7.38 (m, 5H, H_{arom}), 7.43 (d, *J* = 1.8 Hz, 1H, CH=N), 7.70 (d, *J* = 2.2 Hz, 1H, CH—N), 8.55 (d, *J* = 8.6 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.9 (CHPh), 55.1 ($CH_2C{=}O$), 64.5 (CH_2OH), 105.2, 126.9 (3C), 128.1 (2C), 131.4, 138.8, 140.8, 166.3 (C=O). HRMS (FAB^+): calculated for $C_{13}H_{16}N_3O_2$ $[M+H]^+$, *m*/*z* 246.1243; found for $[M+H]^+$, *m*/*z* 246.1244.

4.4.5. (*R*)-*N*-(2-Hydroxy-1-phenylethyl)-2-(1*H*-imidazol-1-yl)acetamide 1k

(120 mg, 84%) as a white solid, mp 180–181 °C. $[\alpha]_D = -105.2$ (*c* 1.0, MeOH). ^1H NMR (400 MHz, DMSO-d_6): δ = 3.47 (bs, 1H, OH), 3.57 (dd, *J* = 9.4, 5.5 Hz, 1H, CH_2OH), 3.61 (dd, *J* = 9.5, 4.0 Hz, 1H, CH_2OH), 4.74 (s, 2H, $CH_2C{=}O$), 4.86 (m, 1H, CHPh), 6.87 (bs, 1H, CH=CH—N), 7.08 (bs, 1H, CH=CH—N), 7.22–7.27 (m, 1H, H_{arom}), 7.30–7.32 (m, 4H, H_{arom}), 7.58 (s, 1H, N=CH—N), 8.68 (d, *J* = 8.2 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 48.8 ($CH_2C{=}O$), 55.3 (CHPh), 64.6 (CH_2OH), 120.4, 126.9 (3C), 127.9, 128.14 (2C), 138.09, 140.7, 166.5 (C=O). HRMS (FAB^+): calculated for $C_{13}H_{16}N_3O_2$ $[M+H]^+$, *m*/*z* 246.1243; found for $[M+H]^+$, *m*/*z* 246.1240.

4.4.6. (*R*)-*N*-(2-Hydroxy-1-phenylethyl)-2-(1*H*-benzo[*d*]-imidazol-1-yl) acetamide 1l

(427 mg, 96%) as a white solid, mp 218–220 °C, $[\alpha]_D = -108.0$ (*c* 1.0, MeOH). ^1H and ^{13}C NMR data are identical to those described in the literature.[11]

4.4.7. *N*-(2-Hydroxyethyl)-2-(1*H*-pyrazol-1-yl)acetamide 1m

(213 mg, 97%) as a white solid, mp 111–112 °C. ^1H NMR (400 MHz, CD_3OD): δ = 3.35 (t, *J* = 5.6 Hz, 2H, CH_2NH), 3.61 (t, *J* = 5.6 Hz, 2H, CH_2OH), 4.89 (s, 2H, $CH_2C{=}O$), 6.36 (t, *J* = 2.2 Hz, 1H, CH=CH—N), 7.56 (d, *J* = 1.8 Hz, 1H, CH=N), 7.70 (d, *J* = 2.2 Hz, 1H, CH—N). ^{13}C NMR (100 MHz, CD_3OD): δ = 41.7 (CH_2NH), 53.6 ($CH_2C{=}O$), 59.9 (CH_2OH), 105.7, 131.7, 139.9, 168.4 (C=O). HRMS (FAB^+): calculated for $C_7H_{12}N_3O_2$ $[M+H]^+$, *m*/*z* 170.0930; found for $[M+H]^+$, *m*/*z* 170.0927.

4.4.8. *N*-(2-Hydroxyethyl)-2-(1*H*-imidazol-1-yl)acetamide 1n

(544 mg, 92%) as a white solid, mp 135–136 °C (literature[12] 132.8–134 °C). ^1H and ^{13}C NMR data are identical to those described in the literature[12] HRMS (FAB^+): calculated for $C_7H_{12}N_3O_2$ $[M+H]^+$, *m*/*z* 170.0930; found for $[M+H]^+$, *m*/*z* 170.0934.

4.4.9. *N*-(2-Hydroxyethyl)-2-(1*H*-benzo[*d*]imidazol-1-yl)acetamide 1o

(187 mg, 87%) as a white solid, mp 211–212 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.18 (q, *J* = 5.8 Hz, 2H, CH_2NH), 3.38 (bs, 1H, OH), 3.44 (m, 2H, CH_2OH), 4.93 (s, 2H, $CH_2C{=}O$), 7.18–7.26 (m, 2H, H_{arom}), 7.44–7.46 (m, 1H, H_{arom}), 7.64–7.66 (m, 1H, H_{arom}), 8.17 (s, 1H, N=CH—N), 8.40 (t, *J* = 5.4 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 42.2 (CH_2NH), 47.3 ($CH_2C{=}O$), 60.1 (CH_2OH), 110.6, 119.8, 121.9, 122.8, 134.8, 143.7, 145.3, 167.1 (N=CH) (C=O). HRMS (CI^+): calculated for $C_{11}H_{14}N_3O_2$ $[M+H]^+$, *m*/*z* 220.1086; found for $[M+H]^+$, *m*/*z* 220.1085.

4.4.10. (*S*)-*N*-(1-Hydroxypropan-2-yl)-2-(1*H*-pyrazol-1-yl)acetamide 1p

(123 mg, 52%) as a white solid, mp 121–122 °C. $[\alpha]_D = -15.3$ (*c* 1.0, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 1.14 (d, *J* = 6.8 Hz, 3H, CH_3), 3.49 (d, *J* = 4.8 Hz, 2H, CH_2OH), 3.94 (m, 1H, $CHCH_3$), 4.84 (s, 2H, $CH_2C{=}O$), 6.33 (m, 1H, CH=CH—N), 7.53 (d, *J* = 1.6 Hz, 1H, CH=N), 7.67 (d, *J* = 2.0 Hz, 1H, CH—N). ^{13}C NMR (100 MHz, CD_3OD): δ = 17.2 (CH_3), 48.9 ($CHCH_3$), 55.2 ($CH_2C{=}O$), 66.0 (CH_2OH), 107.1, 133.2, 141.2, 169.1 (**C**=O). HRMS (FAB^+): calculated for $C_8H_{14}N_3O_2$ $[M+H]^+$, *m*/*z* 184.1086; found for $[M+H]^+$, *m*/*z* 184.1084.

4.4.11. (*S*)-*N*-(1-Hydroxypropan-2-yl)-2-(1*H*-imidazol-1-yl)acetamide 1q

(417 mg, 84%) as a white solid, mp 172–173 °C. $[\alpha]_D = -8.0$ (*c* 1.0, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 1.14 (d, *J* = 6.8 Hz, 3H, CH_3CH), 3.47 (dd, *J* = 11.2, 5.2 Hz, 1H, CH_2OH), 3.51 (dd, *J* = 11.2, 5.2 Hz, 1H, CH_2OH), 3.95 (m, 1H, $CHCH_3$), 4.72 (s, 2H, $CH_2C{=}O$), 6.97 (bs, 1H, CH=CH—N), 7.10 (bs, 1H, CH=CH—N), 7.65 (bs, 1H, N=CH—N). ^{13}C NMR (100 MHz, CD_3OD): δ = 17.1 (CH_3), 30.0 ($CH_2C{=}O$), 50.4 ($CHCH_3$) 66.0 (CH_2OH), 121.9, 129.0, 139.6, 169.0 (C=O). HRMS (FAB^+): calculated for $C_8H_{14}N_3O_2$ $[M+H]^+$, *m*/*z* 184.1086; found for $[M+H]^+$, *m*/*z* 184.1092.

4.4.12. (*S*)-*N*-(1-Hydroxypropan-2-yl)-2-(1*H*-benzo[*d*]-imidazol-1-yl)acetamide 1r

(276 mg, 81%) as a white solid, mp 187–189 °C. $[\alpha]_D = -12.0$ (*c* 1.0, MeOH). ^1H NMR (400 MHz, DMSO-d_6): δ = 1.07 (d, *J* = 6.8 Hz, 3H, CH_3), 3.30 (dd, *J* = 10.6, 5.8 Hz, 1H, CH_2OH), 3.38 (dd, *J* = 10.6, 5.3 Hz, 1H, CH_2OH), 3.79 (m, 1H, $CHCH_3$), 4.91 (AB system, *J* = 16.3 Hz, 2H, $CH_2C{=}O$), 7.17–7.29 (m, 2H, H_{arom}), 7.43–7.46 (m, 1H, H_{arom}) 8.17 (s, 1H, N=CH—N), 8.28 (d, *J* = 7.9 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.0 (CH_3), 46.9 ($CH_2C{=}O$ and CHNH), 64.2 (CH_2OH), 110.2, 119.3, 121.4, 122.3, 134.2, 143.2, 144.9, 165.84 (C=O). HRMS (FAB^+): calculated for $C_{12}H_{16}N_3O_2$ $[M+H]^+$, *m*/*z* 234.1243; found for $[M+H]^+$, *m*/*z* 234.1251.

4.4.13. (*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-2-(1*H*-pyrazol-1-yl)acetamide 1s

(114 mg, 79%) as a white solid, mp 120–122 °C. $[\alpha]_D = -32.0$ (*c* 1.0, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 0.89 (d, *J* = 6.8 Hz, 3H, $(CH_3)_2CH$), 0.93 (d, *J* = 6.8 Hz, 3H, $(CH_3)_2CH$), 1.86 (m, 1H, $CH(CH_3)_2$), 3.54 (dd, *J* = 11.6, 5.2 Hz, 1H, CH_2OH), 3.59 (dd, *J* = 11.2, 4.4 Hz, 1H, CH_2OH), 3.68 (m, 1H, CHN), 4.88 (AB system, *J* = 13.2 Hz, 2H, $CH_2C{=}O$), 6.34 (2d, 1H, CH=CH—N), 7.53 (d, *J* = 1.6 Hz, 1H, CH=N), 7.68 (d, *J* = 2.0 Hz, 1H, CH—N). ^{13}C NMR (100 MHz, CD_3OD): δ = 18.8 (CH_3), 20.1 (CH_3), 30.1 ($CH(CH_3)_2$), 55.2, 58.4, 63.1, 107.2, 133.2, 141.2, 169.7 (C=O). HRMS (FAB^+): calculated for $C_{10}H_{18}N_3O_2$ $[M+H]^+$, *m*/*z* 212.1399; found for $[M+H]^+$, *m*/*z* 212.1406.

4.4.14. (*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-2-(1*H*-imidazol-1-yl)acetamide 1t

(142 mg, 83%) as a white solid, mp 160–161 °C. $[\alpha]_D = -13.8$ (*c* 0.5, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 0.91 (d, *J* = 7.2 Hz, 3H, $(CH_3)_2CH$), 0.94 (d, *J* = 7.2 Hz, 3H, $(CH_3)_2CH$), 1.86 (m, 1H, $CH(CH_3)_2$), 3.55 (dd, *J* = 11.2, 6.4 Hz, 1H, CH_2OH), 3.63 (dd, *J* = 11.6, 4.4 Hz, 1H, CH_2OH), 3.71 (m, 1H, CHN), 4.76 (AB system, *J* = 13.2 Hz, 2H, $CH_2C{=}O$), 6.98 (s, 1H, CH=CH—N), 7.12 (s, 1H, CH=CH—N), 7.67 (s, 1H, N=CH—N). ^{13}C NMR (100 MHz, CD_3OD): δ = 18.9 (CH_3), 20.1 (CH_3), 30.2 [$CH(CH_3)_2$], 50.5 ($CH_2C{=}O$), 58.5 (CHNH), 63.1 (CH_2OH), 121.9, 129.1, 139.6, 169.5 (C=O). HRMS

(FAB$^+$): calculated for $C_{10}H_{18}N_3O_2$ [M+H]$^+$, m/z 212.1399; found for [M+H]$^+$, m/z 212.1393.

4.4.15. (*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-2-(1*H*-benzo[*d*]imidazol-1-yl)acetamide 1u

(365 mg, 94%) as a white solid, mp 213–215 °C. $[\alpha]_D = -8.0$ (c 1.0, MeOH). ^{1}H and ^{13}C NMR data are identical to those described in the literature[11] HRMS (FAB$^+$): calculated for $C_{14}H_{20}N_3O_2$ [M+H]$^+$, m/z 262.1556; found for [M+H]$^+$, m/z 262.1562.

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