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Microwave-assisted conversion of *N*-substituted oxazolidin-2,4-diones into α-hydroxyamides

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Abstract—*N*-Substituted oxazolidin-2,4-diones have been synthesized in a novel one-pot reaction by reacting cyanohydrins stepwise with 1,1′-carbonyldiimidazole and primary amines followed by acidic hydrolysis of the intermediate 4-imino-oxazolidin-2-ones. Their microwave-assisted conversion into α-hydroxyamides was accomplished by treatment with catalytic amounts of sodium methoxide in methanol.

1. Introduction

The α-hydroxyamide moiety is a well known pharmacophore that is present in various biologically active compounds. α-Hydroxyamides have, for example, been identified as inhibitors of methionine aminopeptidase-2 and as HIV protease inhibitors.[1,2] Mycalamides are a class of α-hydroxyamides which exhibit potent antitumour activity.[3] α-Hydroxyamides are as well valuable intermediates in the synthesis of natural products and various biologically active compounds.[4–6] Known methods for their preparation can be divided into four main categories: reactions of carboxylic acids and activated acid derivatives with amines, reduction of α-ketoamides, micellaneous methods and the synthesis of α-hydroxyamides via cyclic precursors.

The conversion of α-hydroxyacids into α-hydroxyamides has been accomplished in moderate to high yields at high temperature, high pressure, Lewis acid catalyzed, by treatment of α-hydroxyacids with *N*-sulfinylanilines and by aminolysis of *O*-TMS-protected acid chlorides.[7–12] Reactions of α-hydroxyesters with amines usually require long reaction times, forcing or enzyme catalyzed reaction conditions.[13] The reduction of α-ketoamides has for instance been accomplished with sodium borohydride, $LiBEt_3H$, $KBEt_3H$, with magnesium- and titanium-based reagents and by catalytic hydrogenation in the presence of palladium on charcoal.[14–17] A novel method for the synthesis of α-hydroxyamides represents the reaction of 2,3-epoxyamides with samarium diiodide.[18] Katritzky reported the synthesis of α-hydroxyamides by treatment of mandelic acid with *N*-(1-methanesulfonyl)benzotriazole and primary amines.[19]

1,3-Dioxolane-2,4-diones, acetonides of α-hydroxycarboxylic acids and oxazolidin-2,4-diones have been used as cyclic precursors in the preparation of α-hydroxyamides.[20–22] Commonly the alkaline hydrolysis of oxazolidin-2,4-diones leads to a mixture of α-carbamoyloxyacid and α-hydroxyamide.[22] Tamariz described the synthesis of two α-hydroxycarboxamides in 34 and 35% yield by alkaline hydrolysis of the corresponding oxazolidin-2,4-diones.[23] Furthermore, Miethchen reported the conversion of a 5,5-disubstituted 3-cyclohexyloxazolidin-2,4-dione into the corresponding α-hydroxy *N*-cyclohexylcarboxamide by refluxing the oxazolidin-2,4-dione in methanol in the presence of an excess of sodium methoxide for 7 h in 97% yield.[24]

Given the importance of the α-hydroxyamide functionality in organic and medicinal chemistry, development of new methods for the efficient synthesis of α-hydroxyamides is still an important challenge. Our group reported the sodium methoxide catalyzed decarbonylation of *O*-substituted 3-hydroxyoxazolidin-2,4-diones, *N*-substituted 3-amino-oxazolidin-2,4-diones and *O*-substituted 3-hydroxy-4-imino oxazolidin-2-ones as novel methods for the synthesis of *O*-substituted α-hydroxyhydroxamic acids, *N*′,*N*′-disubstituted α-hydroxyhydrazides and *O*-substituted α-hydroxyamidoximes.[25] We now report the microwave-assisted conversion of *N*-substituted oxazolidin-2,4-diones into α-hydroxyamides. A comparison of the microwave-

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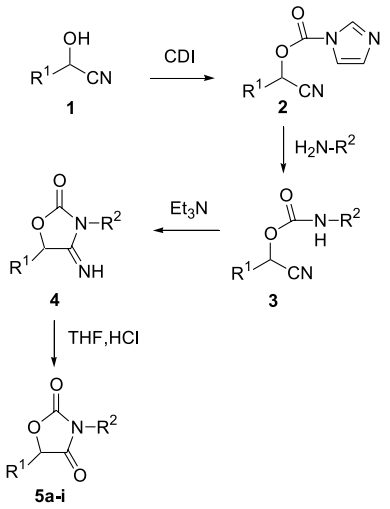
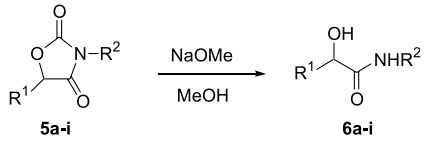


Scheme 1. Synthesis of oxazolidin-2,4-diones (**5a–i**).

Table 1. Synthesis of oxazolidin-2,4-diones (**5a–i**)

5	R^1	R^2	Yield (%)
a	C_6H_5	*m*-FC_6H_4	70
b	1-Naphthyl	*m*-FC_6H_4	70
c	Cyclopropyl	*p*-NCC_6H_4	75
d	2-Thienyl	*p*-$F_3CC_6H_4$	55
e	2-Furyl	*p*-BrC_6H_4	53
f	C_6H_{11}	*p*-ClC_6H_4	68
g	1-Naphthyl	Cyclopropyl	65
h	*p*-MeC_6H_4	*p*-$FC_6H_4CH_2$	67
i	*p*-MeC_6H_4	CH_3	63



Scheme 2. Synthesis of α-hydroxyamides (**6a–i**).

chemistry to the conventional and sealed tube decarbonylation is exemplarily described.

2. Results and discussion

2.1. Synthesis of *N*-substituted oxazolidin-2,4-diones (5a–i)

N-Substituted oxazolidin-2,4-diones (**5**) have been prepared in a novel one pot reaction starting from cyanohydrins (**1**), 1,1′-carbonyldiimidazole (CDI) and primary amines. Reactions of **1** with CDI in dichloromethane furnished imidazolide intermediates **2**. Their treatment with primary amines gave the open-chained carbamate intermediates **3**. Base catalyzed ring closure of **3** furnished 4-imino oxazolidin-2-ones (**4**), which were subsequently hydrolyzed to afford **5** in 53–75% yield (Scheme 1, Table 1).

Due to the characteristic C=O absorption bands of **2–5** the progression of the reaction was readily monitored by IR spectroscopy. *N*-Substituted oxazolidin-2,4-diones (**5**), which have attracted much attention in medicinal and agricultural chemistry,[26] have, for example, previously been prepared from α-hydroxyesters and isocyanates and by reactions of α-hydroxyamides with chloroformates or dialkyl carbonates.[22,26]

2.2. Synthesis of α-hydroxyamides (6a–i)

Microwave-assisted synthesis of **6a–f** was accomplished in high yields of 80–92% by reacting **5a–f** with sodium methoxide (0.2 equiv) in methanol for 3.5–4.5 min (Scheme 2, Table 2). The corresponding reaction of compound **5a** in a sealed tube at 105 °C afforded compound **6a** in 78% yield after 12 min, while conventional heating at atmospheric pressure provided **6a** in 89% yield after 45 min.

Microwave-assisted synthesis of *N*-cyclopropyl, *N*-(4-fluorobenzyl) and *N*-methyl substituted α-hydroxyamides **6g–i** was achieved in moderate to good yields of 55–82% using longer reaction times and harsher reaction conditions. In contrast to the fast microwave-assisted conversion of **5h** into **6h**, the corresponding reaction in a sealed tube at 105 °C took 9 h to give **6h** in only 31% yield. Refluxing **5h** for 35 h in methanol in the presence of sodium methoxide (0.2 equiv) afforded 39% of **6h** (Table 2).

Table 2. Synthesis of α-hydroxyamides (**6a–i**)

6	R^1	R^2	Hold time microwave (min)	Yield (%)	Time conventional	Yield (%)	Time sealed tube	Yield (%)
a	C_6H_5	*m*-FC_6H_4	4.5	90	45 min	89	12 min	78
b	1-Naphthyl	*m*-FC_6H_4	4.5	91	—	—	—	—
c	Cyclopropyl	*p*-NCC_6H_4	4.5	87	—	—	—	—
d	2-Thienyl	*p*-$F_3CC_6H_4$	3.5	80	—	—	—	—
e	2-Furyl	*p*-BrC_6H_4	4	92	—	—	—	—
f	C_6H_{11}	*p*-ClC_6H_4	4.5	84	—	—	—	—
g	1-Naphthyl	Cyclopropyl	14.5	82	—	—	—	—
h	*p*-MeC_6H_4	*p*-$FC_6H_4CH_2$	20	73	35 h	39	9 h	31
i	*p*-MeC_6H_4	CH_3	90	55	—	—	—	—

Microwave reactions were conducted at 100 °C (**6a–g**) or 150 °C (**6h**,**i**) in the presence of 0.2 equiv of sodium methoxide in methanol using microwave glass pressure tubes.

3. Conclusion

We have developed a convenient two-step synthesis for the preparation of α-hydroxyamides using conventional and microwave-assisted chemistry. The first step is a novel one pot-synthesis of *N*-substituted oxazolidin-2,4-diones. In the second step we have demonstrated that *N*-substituted 3-amino-oxazolidin-2,4-diones are valuable precursors for the microwave-assisted synthesis of α-hydroxyamides in moderate to high yields. In comparison to conventional heating at atmospheric pressure and reactions under pressure, the microwave-assisted conversion of *N*-substituted oxazolidin-2,4-diones into α-hydroxyamides proceeds faster and in higher yields. Compared to Shapiro's and Tamariz's methods, the yields of our method are higher, no α-carbamoyloxyacids have been detected and the use of water as a solvent has been avoided. Starting from cyanohydrins our method allows the introduction of different substituents in the α-position of the title compounds. The method is practical and only catalytic amounts of sodium methoxide are necessary for the decarbonylation. The oxazolidin-2,4-dione ring system represents a protecting group for the secondary alcoholic hydroxyl group and the amide nitrogen.

4. Experimental

Cyanohydrins (**1**) have been prepared according to an established literature procedure and were used immediately after structure conformation by IR spectroscopy.[27] Microwave assisted reactions were carried out using a CEM microwave reactor model Discover. Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analysis was carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as solvent.

4.1. General procedure for the preparation of substituted 3-amino-oxazolidin-2,4-diones (5a–i)

A solution of cyanohydrin **1** (5 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise over a period of 10 min to a suspension of 1,1′-carbonyldiimidazole (851 mg, 5.25 mmol) in dry CH_2Cl_2 (5 mL) under ice cooling. After stirring at room temperature for 10 min a solution of the appropriate amine (5 mmol) in dry CH_2Cl_2 (5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. Triethylamine (3 mL) was added and the reaction mixture was stirred until two sharp bands in the IR spectra appeared at 1780–1800 and 1680–1700 cm^{-1}. The solvent was removed under reduced pressure and the residue was dissolved in THF (10 mL). Hydrochloric acid (10 mL, 20%) was added under ice cooling and the reaction mixture was stirred for 50 min. The reaction mixture was extracted thrice with EtOAc (15 mL) and the combined extracts were dried over $MgSO_4$. Removal of the solvent afforded **5a–i** as solids, analytically pure products were obtained after recrystallization from the indicated solvent or purification by column chromatography.

4.1.1. 3-(3-Fluorophenyl)-5-phenyloxazolidin-2,4-dione (5a). Colorless solid (70%). Mp 140 °C (EtOAc–hexane); IR (KBr) ν=1820, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 5.91 (s, 1H), 7.12–7.17 (m, 1H), 7.25–7.33 (m, 2H), 7.44–7.61 (m, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 80.3, 113.4, 116.4, 116.6, 121.3, 121.4, 126.4, 129.7, 130.4, 130.9, 131.1, 131.6, 161.8, 164.3. Anal. Calcd for $C_{15}H_{10}FNO_3$: C, 66.42; H, 3.72; N, 5.16. Found: C, 66.28; H, 3.70; N, 5.18.

4.1.2. 3-(3-Fluorophenyl)-5-(1-naphthyl)oxazolidin-2,4-dione (5b). Colorless solid (70%). Mp 204 °C (THF–Et_2O); IR (KBr) ν=1811, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 6.69 (s, 1H), 7.16 (t, J=7.12 Hz, 1H), 7.31–7.38 (m, 2H), 7.46–7.68 (m, 5H), 7.96 (t, J=8.90 Hz, 2H), 8.10 (d, J=7.89 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 78.6, 113.4, 113.7, 116.4, 116.6, 121.4, 123.5, 124.7, 125.6, 127.1, 127.9, 129.5, 130.9, 131.1, 131.5, 153.5, 167.9. Anal. Calcd for $C_{19}H_{12}FNO_3$: C, 71.03; H, 3.76; N, 4.36. Found: C, 70.93; H, 3.75; N, 4.43.

4.1.3. 3-(4-Cyanophenyl)-5-cyclopropyloxazolidin-2,4-dione (5c). Colorless solid (75%). Mp 163 °C (THF–Et_2O); IR (KBr) ν=2222, 1805, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 0.64–0.89 (m, 4H), 1.32–1.40 (m, 1H), 4.61 (d, J=7.12 Hz, 1H), 7.70 (d, J=8.65 Hz, 2H), 7.80 (d, J=8.65 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 0.3, 9.7, 79.9, 110.5, 115.9, 123.6, 131.2, 132.9, 150.9, 171.5. Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.19; H, 4.20; N, 11.55.

4.1.4. 5-(2-Thienyl)-3-(4-trifluoromethylphenyl)oxazolidin-2,4-dione (5d). Colorless solid (55%). Mp 190 °C (Et_2O–hexane); IR (KBr) ν=1807, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 6.10 (s, 1H), 7.10 (m, 1H), 7.32 (d, J=3.56 Hz, 1H), 7.50 (d, J=6.36 Hz, 1H), 7.68 (d, J=8.65 Hz, 2H), 7.79 (d, J=8.65 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 77.1, 126.0, 126.9, 127.0, 127.1, 128.0, 128.6, 128.8, 132.7, 153.0, 168.9. Anal. Calcd for $C_{14}H_8F_3NO_3S$: C, 51.38; H, 2.46; N, 4.28; S, 9.80. Found: C, 51.21; H, 2.59; N, 4.20; S, 10.00.

4.1.5. 3-(4-Bromophenyl)-5-(2-furyl)oxazolidin-2,4-dione (5e). Brown solid (53%) after column chromatography EtOAc–hexane. Mp 144 °C; IR (KBr) ν=1825, 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 5.91 (s, 1H), 6.47 (dd, J=3.31, 1.78 Hz, 1H), 6.70 (d, J=3.65 Hz, 1H), 7.40 (d, J=8.90 Hz, 2H), 7.53 (m, 1H), 7.65 (d, J=8.90 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 74.5, 111.5, 114.4, 123.4, 127.5, 130.2, 133.1, 143.9, 145.7, 153.4, 167.9. Anal. Calcd for $C_{13}H_8BrNO_4$: C, 48.47; H, 2.50; N, 4.35. Found: C, 48.28; H, 2.59; N, 4.30.

4.1.6. 3-(4-Chlorophenyl)-5-cyclohexyloxazolidin-2,4-dione (5f). Colorless solid (68%). Mp 163 °C (THF–Et_2O); IR (KBr) ν=1805, 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.14–1.40 (m, 5H), 1.64–1.90 (m, 5H), 2.04–2.14 (m, 1H), 4.77 (d, J=3.81 Hz, 1H), 7.38 (d, J=8.90 Hz, 2H), 7.46 (d, J=8.90 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 25.9, 26.0, 26.1, 26.2, 28.7, 40.3, 83.7, 127.1, 129.7, 130.0, 135.1, 154.4, 171.5. Anal. Calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.13; H, 5.59; N, 4.74.

4.1.7. 3-Cyclopropyl-5-(1-naphthyl)oxazolidin-2,4-dione (5g). Colorless solid (65%). Mp 139 °C (THF–Et_2O). IR (KBr) ν=1811, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.02–1.11 (m, 4H), 2.77–2.83 (m, 1H), 6.43 (s, 1H), 7.44–7.50 (m, 2H), 7.54–7.63 (m, 2H), 7.89–7.93 (m, 2H), 8.03 (d, J=8.65 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 5.4, 5.5, 23.5, 77.9, 123.6, 124.4, 125.5, 126.9, 127.6, 127.9, 129.4, 131.1, 131.3, 134.4, 155.6, 171.9. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.81; H, 5.01; N, 5.26.

4.1.8. 3-(4-Fluorobenzyl)-5-(4-methylphenyl)oxazolidin-2,4-dione (5h). Colorless solid (67%). Mp 130 °C (THF–Et_2O); IR (KBr) ν=1809, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 2.36 (s, 3H), 4.68 (s, 2H), 5.68 (s, 1H), 7.02 (t, J=8.65 Hz, 2H), 7.19–7.23 (m, 4H), 7.40 (d, J=8.14 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.7, 43.7, 80.9, 116.2, 116.4, 126.5, 128.8, 130.3, 130.9, 131.2, 131.3, 140.5, 164.4, 171.5. Anal. Calcd for $C_{17}H_{14}FNO_3$: C, 68.22; H, 4.71; N, 4.68. Found: C, 68.29; H, 4.93; N, 4.80.

4.1.9. 3-Methyl-5-(4-methylphenyl)oxazolidin-2,4-dione (5i). Colorless solid (63%). Mp 111 °C (THF–Et_2O); IR (KBr) ν=1805, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 2.37 (s, 3H), 3.13 (s, 3H), 5.71 (s, 1H), 7.20 (d, J=8.13 Hz, 2H), 7.30 (d, J=8.13 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.7, 26.6, 80.9, 126.4, 128.9, 130.2, 140.4, 155.8, 171.8. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.25; H, 5.43; N, 6.80.

4.2. Microwave-assisted synthesis of 6a–i

Compound **5a–i** (0.5 mmol) and sodium methoxide (0.1 mmol) were weighed in a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar. Methanol (5 mL) was added, the tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation for the indicated time (Table 2) using parameters A and B. The reaction mixture was allowed to cool to room temperature and transferred to a round bottom flask. The solvent was evaporated, water (0.5 mL) was added and the mixture was treated thrice with dichloromethane (15 mL). The combined extracts were dried over $MgSO_4$ and the solution was concentrated to 0.5 mL. Addition of Et_2O and hexane provided **6a–i** as solid compounds.

Parameters A. For compounds **6a–g**: Discover mode; power: 200 W; ramp time: 30 s; hold time: as indicated in Table 2; temperature: 100 °C; pressure: 12 bar; PowerMax-cooling.

Parameters B. For compound **6h,i**: Discover mode, power: 250 W; ramp time: 30 s; hold time: as indicated in Table 2; temperature: 150 °C; pressure: 15 bar, PowerMax-cooling.

Synthesis of **6a,h** *in a sealed tube*. Sodium methoxide (0.1 mmol) was added to a stirred solution of **5a,h** (0.5 mmol) in methanol (5 mL). After being refluxed at 105 °C in a sealed tube for the indicated time (Table 2), the solvent was evaporated, water (0.5 mL) was added and the mixture was extracted thrice with dichloromethane (15 mL). The combined extracts were dried over $MgSO_4$ and the solution was concentrated to 0.5 mL. Addition of Et_2O and hexane provided **6a,h** as solid compounds.

Conventional method for the synthesis of **6a,h**. Sodium methoxide (0.1 mmol) was added to a stirred solution of **5a,h** (0.5 mmol) in methanol (5 mL). After being refluxed for the indicated time (Table 2), the solvent was evaporated, water (0.5 mL) was added and the mixture was extracted thrice with dichloromethane (15 mL). The combined extracts were dried over $MgSO_4$ and the solution was concentrated to 0.5 mL. Addition of Et_2O and hexane provided **6a,h** as solid compounds.

4.2.1. *N*-(3-Fluorophenyl)-2-hydroxy-2-phenylacetamide (6a). *Parameter A*. Colorless solid (90%). Mp 163 °C (Et_2O–hexane); IR (KBr) ν=3302, 3229, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 3.50 (s, 1H), 5.87 (s, 1H), 7.12–7.17 (m, 1H), 7.25–7.33 (m, 2H), 7.44–7.61 (m, 6H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 80.3, 113.4, 116.4, 116.6, 121.3, 121.4, 126.4, 129.7, 130.3, 130.9, 131.1, 131.7, 170.1. Anal. Calcd for $C_{14}H_{12}FNO_2$: C, 68.56, H, 4.93; N, 5.71. Found: C, 68.43; H, 5.01; N, 5.56.

4.2.2. *N*-(3-Fluorophenyl)-2-hydroxy-2-(1-naphthyl)-acetamide (6b). *Parameter A*. Colorless solid (91%). Mp 175 °C (Et_2O–hexane); IR (KBr) ν=3302, 3229, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 3.51 (s, 1H), 5.83 (s, 1H), 6.81 (t, J=8.41 Hz, 1H), 7.11 (d, J=9.16 Hz, 1H), 7.20–7.27 (m, 1H), 7.46–7.62 (m, 5H), 7.89–7.92 (m, 2H), 8.12 (s, 1H), 8.19 (d, J=8.41 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 80.3, 113.4, 113.6, 116.4, 116.6, 121.4, 126.4, 129.7, 130.5, 130.9, 131.1, 131.6, 132.4, 132.5, 153.8, 161.8, 164.3, 170.0. Anal. Calcd for $C_{18}H_{14}FNO_2$: C, 73.21; H, 4.78; N, 4.74. Found: C, 73.21; H, 4.79; N, 4.86.

4.2.3. *N*-(4-Cyanophenyl)-2-cyclopropyl-2-hydroxy-acetamide (6c). *Parameter A*. Colorless solid (87%). Mp 120 °C (Et_2O–hexane); IR (KBr) ν=3462, 3317, 2218, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 0.69–0.78 (m, 4H), 1.20–1.28 (m, 1H), 2.80 (s, 1H), 3.72 (d, J=7.89 Hz, 1H), 7.63 (d, J=8.65 Hz, 2H), 7.75 (d, J=8.65 Hz, 2H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 2.6, 3.4, 16.3, 76.0, 107.7, 119.2, 120.0, 133.8, 141.8, 171.8. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.43; H, 5.72; N, 12.89.

4.2.4. 2-Hydroxy-2-(2-thienyl)-*N*-(4-trifluoromethyl-phenyl)acetamide (6d). *Parameter A*. Colorless solid (80%). Mp 196 °C (Et_2O–hexane); IR (KBr) ν=3292, 3111, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 3.35 (s, 1H), 5.63 (s, 1H), 7.04 (t, J=3.56 Hz, 1H), 7.23 (d, J=3.31 Hz, 1H), 736 (d, J=5.09 Hz, 1H), 7.60 (d, J=8.65 Hz, 2H), 7.70 (d, J=8.65 Hz, 2H), 8.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 71.3, 119.9, 126.8, 127.1, 127.6, 130.7, 137.1, 138.4, 140.7, 172.1. Anal. Calcd for $C_{13}H_{10}F_3NO_2S$: C, 51.83; H, 3.35; N, 4.65; S, 10.64. Found: C, 51.75; H, 3.21; N, 4.50; S, 10.49.

4.2.5. *N*-(4-Bromophenyl)-2-(2-furyl)-2-hydroxyacetamide (6e). *Parameter A*. Colorless solid (92%). Mp 162 °C (Et_2O–hexane); IR (KBr) ν=3281, 3163, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 3.34 (s, 1H), 5.29 (s, 1H), 6.40 (dd, J=3.31, 1.78 Hz, 1H), 6.55 (d,

J=3.31 Hz, 1H), 7.44–7.49 (m, 5H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 68.8, 109.7, 111.3, 117.9, 121.9, 132.5, 140.0, 174.6. Anal. Calcd for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.52; H, 3.51; N, 4.75.

4.2.6. *N*-(4-Chlorophenyl)-2-cyclohexyl-2-hydroxyacetamide (6f). *Parameter A*. Colorless solid (84%). Mp 145 °C (Et_2O–hexane); IR (KBr) ν=3315, 3111, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.10–1.33 (m, 5H), 1.65–1.81 (m, 5H), 1.91–1.97 (m, 1H), 2.37 (s, 1H), 4.09 (d, J=3.31 Hz, 1H), 7.29 (d, J=8.90 Hz, 2H), 7.57 (d, J=8.90 Hz, 2H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 26.2, 26.3, 26.4, 26.7, 30.0, 42.1, 77.1, 121.4, 129.5, 129.9, 136.2, 171.6. Anal. Calcd for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.60; H, 6.89; N, 5.17.

4.2.7. *N*-Cyclopropyl-2-hydroxy-2-(1-naphthyl)acetamide (6g). *Parameter A*. Colorless solid (82%). Mp 103 °C (Et_2O–hexane); IR (KBr) ν=3315, 3111, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 0.31–0.72 (m, 4H), 2.68–2.70 (m, 1H), 3.46 (s, 1H), 5.49 (s, 1H), 6.05 (s, 1H), 7.43–7.62 (m, 4H), 7.86 (t, J=8.64 Hz, 2H), 8.06 (d, J=6.11 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 6.8, 7.1, 23.1, 73.3, 124.2, 125.7, 126.5, 127.2, 127.4, 129.3, 130.1, 131.5, 134.7, 134.9, 174.6. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.60; H 6.15; N, 5.90.

4.2.8. *N*-(4-Fluorobenzyl)-2-hydroxy-2-(4-methylphenyl)acetamide (6h). *Parameter B*. Colorless solid (73%). Mp 125 °C (Et_2O–hexane); IR (KBr) ν=3134, 3132, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.34 (s, 3H), 3.44 (s, 1H), 4.38 (m, 2H), 5.01 (s, 1H), 6.65 (s, 1H), 6.97 (t, J=8.65 Hz, 2H), 7.13–7.17 (m, 4H), 7.26 (d, J=8.14 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.6, 43.2, 74.5, 115.9, 116.1, 127.2, 129.7, 129.8, 130.0, 134.0, 136.8, 139.1, 163.8, 172.7. Anal. Calcd for $C_{16}H_{16}FNO_2$: C, 70.32; H, 5.90; N, 5.12. Found: C, 70.19; H, 5.77; N, 5.10.

4.2.9. 2-Hydroxy-*N*-methyl-2-(4-methylphenyl)acetamide (6i). *Parameter B*. Colorless solid (55%). Mp 96 °C (Et_2O–hexane); IR (KBr) ν=3337, 3198, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.34 (s, 3H), 2.80 (d, J=4.80 Hz, 3H), 3.45 (s, 1H), 4.97 (s, 1H), 6.21 (s, 1H), 7.17 (d, J=8.13 Hz, 2H), 7.26 (d, J=8.13 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.6, 26.7, 74.4, 127.2, 129.90, 129.93, 136.9, 138.9, 173.5. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.13; H, 7.20; N, 7.85.

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