

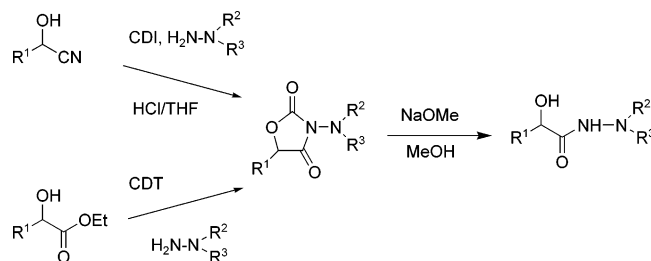
Conventional and Microwave-Assisted Conversion of Substituted 3-Amino-oxazolidin-2,4-diones into *N,N'*-Disubstituted α -Hydroxyhydrazides

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Substituted 3-amino-oxazolidin-2,4-diones have been prepared by reacting cyanohydrins or α -hydroxyesters subsequently with 1,1'-carbonyldiimidazole and 1,1-disubstituted hydrazines followed by acidic hydrolysis in case of the intermediate 3-amino-4-imino-oxazolidin-2-ones. Conventional and microwave-assisted syntheses of *N,N'*-disubstituted α -hydroxyhydrazides have been accomplished by reacting substituted 3-amino-oxazolidin-2,4-diones with catalytic amounts of sodium methoxide in methanol.

Introduction

N,N'-Disubstituted α -hydroxyhydrazides are α -functionalized carboxylic acid hydrazide derivatives. Considerable research effort has been dedicated to the preparation of *N,N'*-disubstituted α -hydroxyhydrazides. However, in comparison to mono- and unsubstituted hydrazides, far fewer general synthetic methods and applications are known.¹ *N,N'*-Dialkyl carboxylic acid hydrazides are useful intermediates in the preparation of amine imides and polysubstituted hydrazines.² Some examples of biologically active *N,N'*-disubstituted hydrazides have been reported.^{3,4} The most important methods for the preparation of *N,N'*-disubstituted hydrazides are *N,N'*-dicyclohexylcarbodiimide-mediated coupling reactions of carboxylic acids with 1,1-disubstituted hydrazines and the acylation of 1,1-disubstituted hydrazines with acid chlorides.⁴⁻⁷ Another approach reported

by Katritzky utilizes the benzotriazole methodology, starting from 1-acyl-2-arylhydrazines and 1-(1-hydroxymethyl)benzotriazole followed by treatment of the benzotriazole-containing intermediates with NaBH_4 , Grignard reagents, or lithium acetylides.² Kollar described a homogeneous palladium-catalyzed hydrazinocarbonylation for the synthesis of *N,N'*-disubstituted steroidal hydrazides.³ A single reaction of a lipase-catalyzed hydrazinolysis of ethyl acetate with *N*-methyl-*N'*-phenylhydrazine has been reported by Gotor.⁸ The acylation of 1,1-disubstituted hydrazines with esters gives only poor yields or does not work at all.⁹ However, 1,1-dimethylhydrazine does react with more reactive esters such as methyl formate and ethyl oxalate.⁹ Because of the relatively weak nucleophilic nature of 1,1-disubstituted hydrazines and the presence of an alcoholic functionality in the starting materials, most of the methods described above cannot be applied for the synthesis of *N,N'*-disubstituted α -hydroxyhydrazides. Their synthesis is

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still difficult, and relatively few examples are known. Most of the α -hydroxyhydrazides described in the literature contain a tertiary alcoholic functionality and have been prepared by the treatment of α -ketohydrazides with Grignard reagents.¹⁰ Teleha reported a multistep synthesis of two α -hydroxyhydrazides with a secondary alcoholic functionality by reacting an *O*-TMS-protected α -hydroxyester with either 4-aminomorpholine or 1-aminopiperidine in the presence of trimethylaluminum.¹¹ The lack of an efficient and general method for the preparation of *N,N'*-disubstituted α -hydroxyhydrazides prompted us to investigate the applicability of substituted 3-amino-oxazolidin-2,4-diones as precursors for the synthesis of the title compounds. In two previous publications, we reported the sodium methoxide-catalyzed decarbonylation of *O*-substituted 3-hydroxy-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 and *O*-substituted α -hydroxyamidoximes, respectively.^{12,13} We can now successfully extend our novel decarbonylation methodology to the conventional and microwave-assisted synthesis of *N,N'*-disubstituted α -hydroxycarboxylic acid hydrazides.

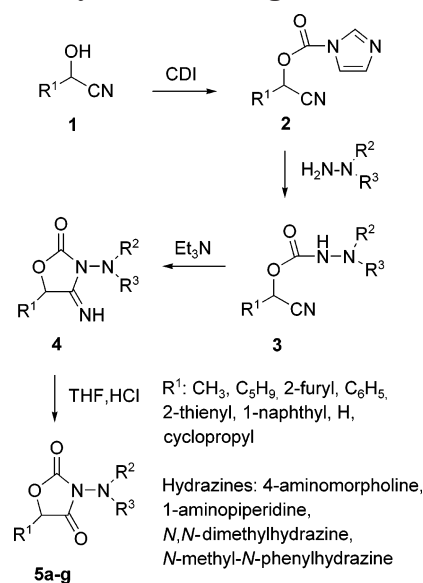
Results and Discussion

Synthesis of Substituted 3-Amino-oxazolidin-2,4-diones (5a–g). 3-Amino-oxazolidin-2,4-diones (**5a–g**) were accessible in a novel one-pot reaction starting from cyanohydrins (**1**), as previously described for the synthesis of *O*-substituted 3-hydroxy-oxazolidin-2,4-diones.¹² Treatment of **1** with 1,1'-carbonyldiimidazole (CDI) in dichloromethane smoothly led to CDI-activated cyanohydrins (**2**), which were reacted with 1,1-disubstituted hydrazines to give open-chained carbazate intermediates (**3**). Base-catalyzed ring closure of **3** gave 3-amino-4-imino-oxazolidin-2-ones (**4**). Finally, acidic hydrolysis of **4a–g** afforded **5a–g** in 65–75% yield.

Synthesis of Substituted 3-Amino-oxazolidin-2,4-diones (5h–l). However, the use of glycolonitrile and commercially available mandelonitrile provided compounds **5j** and **5l** in only 29 (**5j**) and 47% (**5l**) yield, respectively. Therefore, we turned our attention to ethyl mandelate (**6a**) and ethyl glycolate (**6b**) as starting materials. Their successive treatment with 1,1'-carbonyldiimidazole (CDI) and 1,1-disubstituted hydrazines afforded compounds **5h–l** in higher yields of 50–69% (Scheme 2, Table 1).¹⁴

Substituted 3-amino-oxazolidin-2,4-diones have also been prepared previously in moderate to good yields by subsequent treatment of α -hydroxycarboxylic acid esters with phosgene or azolides and hydrazines by carbonylation of *N'*-monosubstituted 2-hydroxycarboxylic acid hydrazides and by reactions of 1,3,4-dioxazin-2,5-diones

SCHEME 1. Synthesis of 5a–g



SCHEME 2. Synthesis of 5h–l

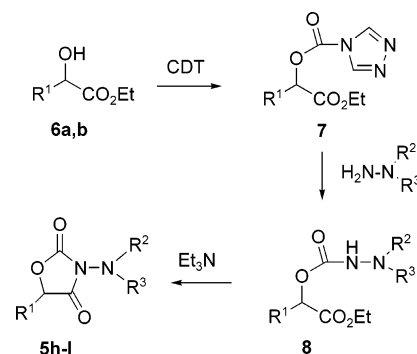


TABLE 1. Synthesis of 5a–l

5	R ¹	R ²	R ³	yield (%)
a	CH ₃	–(CH ₂) ₅ –		68
b	cyclopropyl	–(CH ₂) ₅ –		70
c	cyclopropyl	–CH ₂ CH ₂ OCH ₂ CH ₂ –		73
d	C ₅ H ₉	CH ₃	C ₆ H ₅	75
e	2-thienyl	–CH ₂ CH ₂ OCH ₂ CH ₂ –		71
f	2-furyl	–CH ₂ CH ₂ OCH ₂ CH ₂ –		67
g	1-naphthyl	CH ₃	CH ₃	65
h	C ₆ H ₅	CH ₃	C ₆ H ₅	50
i	C ₆ H ₅	CH ₃	CH ₃	51
j	C ₆ H ₅	–(CH ₂) ₅ –		69
k	C ₆ H ₅	–CH ₂ CH ₂ OCH ₂ CH ₂ –		68
l	H	–(CH ₂) ₅ –		62

with hydrazines.^{14,15} A well-known 3-amino-oxazolidin-2,4-dione represents the broad-spectrum fungicide Famoxadone, which is particularly active against grape downy mildew as well as potato and tomato late and early blights.¹⁶

Synthesis of *N,N'*-Disubstituted α -Hydroxyhydrazides (9a–l). Next, we investigated the conventional and microwave-assisted conversion of **5** into **9**. According

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SCHEME 3. Synthesis of 9a–l

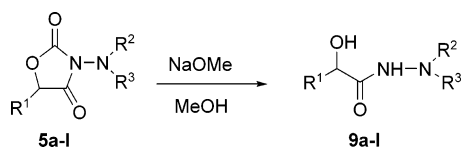


TABLE 2. Conventional and Microwave-Assisted Synthesis of 9a–l

9	R ¹	R ²	R ³	yield (%) conv	yield (%) mw
a	CH ₃	–(CH ₂) ₅ –		63 ^a	
b	cyclopropyl	–(CH ₂) ₅ –		79 ^a	91 ^a
c	cyclopropyl	–CH ₂ CH ₂ OCH ₂ CH ₂ –		80 ^a	
d	C ₅ H ₉	CH ₃	C ₆ H ₅	80 ^a	
e	2-thienyl	–CH ₂ CH ₂ OCH ₂ CH ₂ –		67 ^a	68 ^a
f	2-furyl	–CH ₂ CH ₂ OCH ₂ CH ₂ –		67 ^a	
g	1-naphthyl	CH ₃	CH ₃	78 ^a	81 ^a
h	C ₆ H ₅	CH ₃	C ₆ H ₅	66 ^a	80 ^a
i	C ₆ H ₅	CH ₃	CH ₃	63 ^a	63 ^a
j	C ₆ H ₅	–(CH ₂) ₅ –		76 ^a	
k	C ₆ H ₅	–CH ₂ CH ₂ OCH ₂ CH ₂ –		75, ^a 74, ^b 72 ^c	76 ^a
l	H	–(CH ₂) ₅ –		75 ^a	

^a 0.2 equiv. ^b 0.1 equiv. ^c 0.4 equiv of sodium methoxide.

to previous results obtained during the decarbonylation of *O*-substituted 3-hydroxy-4-imino-oxazolidin-2-ones and *O*-substituted 3-hydroxy-oxazolidin-2,4-diones, the conventional conversion of **5a–l** into **9a–l** was accomplished in good yields of 63–80% within 45 min by refluxing compounds **5a–l** in the presence of sodium methoxide (0.2 equiv) in methanol.^{12,13} Furthermore, microwave-assisted synthesis of **9b**, **e**, **g–i**, and **k** was achieved within 4.5 min in comparable or higher yields of 63–91% in the presence of sodium methoxide (0.2 equiv) in methanol. Next, the effect of the amount of sodium methoxide on yields and reaction times has been studied in two additional experiments. Treatment of **5k** with sodium methoxide (0.1 equiv) under conventional reaction conditions for 90 min afforded compound **9k** in 74% yield. The reaction of compound **5k** with sodium methoxide (0.4 equiv) in methanol provided **9k** in 72% yield. (Scheme 3, Table 2).

In contrast to the smooth decarbonylation of *O*-substituted 3-hydroxy-4-imino-oxazolidin-2-ones in the presence of sodium methoxide (0.2 equiv) in methanol, no reaction took place when 5-cyclopropyl-4-imino-3-morpholin-4-yl-oxazolidin-2-one (**4c**) was reacted under similar conventional or microwave-assisted reaction conditions.¹³ The structures of all of the compounds were confirmed by IR spectra, ¹H and ¹³C NMR spectra, and elemental analysis.

Conclusions

We have developed a novel and convenient two-step method for the preparation of *N,N'*-disubstituted α -hydroxyhydrazides (**9**). The first step represents a novel and practical one-pot protocol for the preparation of substituted 3-amino-oxazolidin-2,4-diones (**5**). The second step involves the previously unreported conventional and microwave-assisted decarbonylation of substituted 3-amino-oxazolidin-2,4-diones. The microwave-assisted synthesis of compounds **9b**, **e**, **g–i**, and **k** proceeds faster than the conventional reactions, and the yields are

comparable or higher. Starting from cyanohydrins and α -hydroxyesters, which are commercially available or readily accessible, our method allows the introduction of different substituents in the α position of the α -hydroxyhydrazides (**9**). Oxazolidin-2,4-dione serves not only as a precursor for the α -hydroxyhydrazide moiety but also as a protecting group for the secondary alcoholic hydroxyl group and the hydrazide nitrogen. The smooth decarbonylation of compound **5k** in the presence of 0.1 equiv of sodium methoxide may be an advantage in the presence of other functional groups in the case of more complex compounds. However, the decarbonylation in the presence of 0.2 equiv proceeds faster and was therefore chosen as the standard method.

Experimental Section

Dichloromethane was distilled over calcium chloride prior to use. Cyanohydrins (**1**) have been prepared according to an established literature procedure and were used immediately after structure confirmation by IR spectroscopy.¹⁷ Ethyl glycolate (**6a**) and ethyl mandelate (**6b**) were purchased and used as received.

Procedure for the Preparation of 5-Cyclopropyl-4-imino-3-morpholin-4-yl-oxazolidin-2-one (4c) and Substituted 3-Amino-oxazolidin-2,4-diones (5a–g). A solution of cyanohydrin **1** (5 mmol) in dry CH₂Cl₂ (5 mL) was added dropwise over a period of 10 min to a suspension of 1,1'-carbonyldiimidazole (5.5 mmol) in dry CH₂Cl₂ (5 mL) under ice cooling. After stirring at room temperature for 10 min, a solution of the appropriate hydrazine (5 mmol) in dry CH₂Cl₂ (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 for 4–6 h until two sharp bands appeared in the IR spectra at 1780–1800 and 1680–1700 cm⁻¹. In the case of compound **4c**, EtOAc (30 mL) was added, and the organic layer was washed with water (3 × 10 mL), dried over MgSO₄, and evaporated. Crystallization from EtOAc–hexane afforded compound **4c** in 78% yield.

In the case of compounds **5a–g**, the solvent was removed under reduced pressure, and the residue was dissolved in THF (3 mL). Hydrochloric acid (10 mL, 20%) was added under ice cooling, and the reaction mixture was stirred for 45 min. The reaction mixture was extracted thrice with EtOAc (15 mL), and the combined extracts were dried over MgSO₄. Removal of the solvent afforded **5a–g** as solids that were recrystallized from EtOAc–hexane.

5-Cyclopropyl-4-imino-3-morpholin-4-yl-oxazolidin-2-one (4c). Colorless solid (78%); mp 104 °C (EtOAc–hexane); IR (KBr): 1790, 1680 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.64–0.89 (m, 4H), 1.32–1.40 (m, 1H), 3.35 (t, *J* = 4.60 Hz, 4H), 3.80 (t, *J* = 4.60 Hz, 4H), 4.50 (d, *J* = 6.87 Hz, 1H), 7.49 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 0.6, 10.3, 51.4, 66.6, 76.9, 152.8, 156.9; Anal. Calcd for C₁₀H₁₅N₃O₃: C, 53.32; H, 6.71; N, 18.65. Found: C, 53.04; H, 6.95; N, 18.78.

5-Methyl-3-piperidin-1-yl-oxazolidin-2,4-dione (5a). Colorless solid (68%); mp 79 °C (EtOAc–hexane); IR (KBr): 1825, 1747 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.45–1.60 (m, 2H), 1.68 (d, *J* = 6.86 Hz, 3H), 1.72–1.77 (m, 4H), 3.23 (t, *J* = 5.60 Hz, 4H), 4.78 (q, *J* = 6.86 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 10.1, 23.3, 26.2, 50.2, 78.8, 152.9, 170.0; Anal. Calcd for C₉H₁₄N₂O₃: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.69; H, 7.32; N, 14.31.

5-Cyclopropyl-3-piperidin-1-yl-oxazolidin-2,4-dione (5b). Colorless solid (70%); mp 78 °C (EtOAc–hexane); IR (KBr): 1824, 1747 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.62–0.80 (m, 4H), 1.20–1.28 (m, 1H), 1.43–1.60 (m, 2H), 1.71–1.77 (m, 4H), 3.23 (t, *J* = 5.60 Hz, 4H), 4.41 (d, *J* = 6.86 Hz, 1H); ¹³C NMR

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(100 MHz, CDCl₃): δ 0.5, 10.1, 23.2, 26.3, 50.1, 78.9, 153.6, 169.7; Anal. Calcd for C₁₁H₁₆N₂O₃: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.79; H, 7.31; N, 12.57.

5-Cyclopropyl-3-morpholin-4-yl-oxazolidin-2,4-dione (5c). Colorless solid (73%); mp 119 °C (EtOAc–hexane); IR (KBr): 1820, 1741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.51–0.81 (m, 4H), 1.21–1.29 (m, 1H), 3.31 (t, J = 4.57 Hz, 4H), 3.84 (t, J = 4.57 Hz, 4H), 4.42 (d, J = 6.86 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 0.5, 10.1, 50.3, 65.3, 78.4, 151.5, 168.5; Anal. Calcd for C₁₀H₁₄N₂O₄: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.94; H, 6.32; N, 12.41.

5-Cyclopentyl-3-(*N*-methyl-*N*-phenylamino)-oxazolidin-2,4-dione (5d). Colorless solid (75%); mp 68 °C (EtOAc–hexane); IR (KBr): 1824, 1757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.45–1.90 (m, 8H), 2.46–2.56 (m, 1H), 3.33 (s, 3H), 4.87 (d, J = 5.08 Hz, 1H), 6.89 (d, J = 7.63 Hz, 2H), 6.97 (t, J = 7.38 Hz, 1H), 7.26–7.31 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 25.6, 25.7, 28.5, 39.9, 41.4, 81.2, 114.3, 122.2, 129.8, 147.1, 153.5, 170.7; Anal. Calcd for C₁₅H₁₈N₂O₃: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.77; H, 6.83; N, 10.19.

3-Morpholin-4-yl-5-(2-thienyl)-oxazolidin-2,4-dione (5e). Colorless solid (71%); mp 158 °C (EtOAc–hexane); IR (KBr): 1810, 1751 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.36 (t, J = 4.84 Hz, 4H), 3.85 (t, J = 4.84 Hz, 4H), 5.92 (s, 1H), 7.08 (t, J = 3.82 Hz, 1H), 7.24 (d, J = 3.56 Hz, 1H), 7.45 (d, J = 5.09 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 52.2, 67.1, 75.5, 127.9, 128.5, 128.6, 133.0, 152.6, 168.4; Anal. Calcd for C₁₁H₁₂N₂O₄S: C, 49.25; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.20; H, 4.59; N, 10.39; S, 11.96.

5-(2-Furyl)-3-morpholin-4-yl-oxazolidin-2,4-dione (5f). Brown solid (67%); mp 149 °C (EtOAc–hexane); IR (KBr): 1820, 1751 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.39 (t, J = 4.84 Hz, 4H), 3.87 (t, J = 4.84 Hz, 4H), 5.70 (s, 1H), 6.44 (dd, J = 1.78, 3.31 Hz, 1H), 6.65 (d, J = 3.30 Hz, 1H), 7.49 (d, J = 1.27 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 52.2, 67.1, 73.0, 111.4, 114.3, 144.0, 145.6, 152.8, 167.2; Anal. Calcd for C₁₁H₁₂N₂O₅: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.27; H, 4.89; N, 11.06.

3-Dimethylamino-5-naphth-1-yl-oxazolidin-2,4-dione (5g). Colorless solid (65%); mp 115 °C (EtOAc–hexane); IR (KBr): 1820, 1751 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.00 (s, 6H), 6.45 (s, 1H), 7.47–7.64 (m, 4H), 7.89–7.96 (m, 2H), 8.02 (d, J = 8.39 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 44.7, 77.3, 123.5, 124.6, 125.6, 127.0, 127.6, 127.7, 129.4, 131.3, 134.4, 153.5, 169.7; Anal. Calcd for C₁₅H₁₄N₂O₃: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.56; H, 5.32; N, 10.38.

General Procedure for the Preparation of Substituted 3-Amino-oxazolidin-2,4-diones (5h–l). A solution of α -hydroxycarboxylic acid esters **6a** and **b** (5 mmol) in dry CH₂Cl₂ (5 mL) was added dropwise to a suspension of 1,1'-carbonyldi-(1,2,4-triazole) (5.5 mmol) in dry CH₂Cl₂ (10 mL) under ice cooling. After stirring at room temperature for 30 min, a solution of the appropriate hydrazine (5 mmol) in dry CH₂Cl₂ (5 mL) was added, and the reaction mixture was stirred for an additional hour. Triethylamine (0.1 mL) was added, and the reaction mixture was refluxed for 90 min. The organic layer was washed with water, dried over MgSO₄, and filtered. Removal of the solvent and crystallization from EtOAc–hexane afforded **5h–l** as solid compounds.

3-(*N*-Methyl-*N*-phenylamino)-5-phenyl-oxazolidin-2,4-dione (5h). Colorless solid (50%); mp 106 °C (Et₂O–hexane); IR (KBr): 1824, 1750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.36 (s, 3H), 5.86 (s, 1H), 6.79 (d, J = 7.89 Hz, 2H), 6.98 (t, J = 7.37 Hz, 1H), 7.26–7.32 (m, 2H), 7.46–7.51 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 39.9, 79.6, 114.3, 122.4, 126.4, 129.8, 129.9, 130.5, 131.4, 147.0, 153.0, 169.0; Anal. Calcd for C₁₆H₁₄N₂O₃: C, 68.08; H, 5.00; N, 9.92. Found: C, 68.00; H, 5.10; N, 10.01.

3-Dimethylamino-5-phenyl-oxazolidin-2,4-dione (5i). Colorless solid (51%); mp 134 °C (EtOAc–hexane); IR (KBr): 1820, 1755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.96 (s, 6H), 5.67 (s, 1H), 7.39–7.47 (m, 5H); ¹³C NMR (100 MHz, CDCl₃):

δ 44.6, 79.1, 126.4, 129.6, 130.4, 131.7, 153.4, 169.5; Anal. Calcd for C₁₁H₁₂N₂O₃: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.05; H, 5.58; N, 12.67.

5-Phenyl-3-piperidin-1-yl-oxazolidin-2,4-dione (5j). Colorless solid (69%); mp 114 °C (EtOAc–hexane); IR (KBr): 1818, 1750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.42–1.53 (m, 2H), 1.70–1.82 (m, 4H), 3.18–3.32 (m, 4H), 5.65 (s, 1H), 7.32–7.62 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 23.2, 26.2, 53.1, 78.8, 126.4, 129.6, 130.3, 132.0, 153.6, 169.7; Anal. Calcd for C₁₄H₁₆N₂O₃: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.41; H, 6.45; N, 11.00.

3-Morpholin-4-yl-5-phenyl-oxazolidin-2,4-dione (5k). Colorless solid (68%); mp 160 °C (EtOAc–hexane); IR (KBr): 1824, 1747 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.34 (t, J = 5.07 Hz, 4H), 3.84 (t, J = 5.07 Hz, 4H), 5.68 (s, 1H), 7.39–7.47 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 52.2, 67.1, 78.9, 126.3, 129.6, 130.4, 131.6, 153.2, 169.4; Anal. Calcd for C₁₃H₁₄N₂O₄: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.52; H, 5.56; N, 10.54.

3-Piperidin-1-yl-oxazolidin-2,4-dione (5l). Colorless solid (62%); mp 85 °C (Et₂O–hexane); IR (KBr): 1815, 1755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.45–1.61 (m, 2H), 1.72–1.78 (m, 4H), 3.24 (t, J = 5.60 Hz, 4H), 4.65 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 23.2, 26.3, 50.2, 78.9, 153.5, 169.8; Anal. Calcd for C₈H₁₂N₂O₃: C, 52.17; H, 6.57; N, 15.31. Found: C, 52.26; H, 6.85; N, 15.31.

Conventional Method for the Synthesis of 9a–l. NaOMe (0.20 mmol) was added to a stirred solution of **5a–l** (1 mmol) in methanol (30 mL), and the reaction mixture was refluxed for 45 min. The solvent was evaporated, citric acid (0.5 mL, 5%) was added, and the mixture was treated thrice with dichloromethane (15 mL). The combined extracts were dried over MgSO₄, and the solution was concentrated to 0.5 mL. Addition of Et₂O and hexane provided **9a–l** as colorless solids.

Microwave-Assisted Synthesis of 9b, e, g–i, and k. 5b, e, g–i, and k (0.5 mmol) and sodium methoxide (0.1 mmol) were weighed in a 10-mL glass pressure microwave tube equipped with a magnetic stir bar. Methanol (5 mL) was added, the tube was closed with a silicon septum, and the reaction mixture was subjected to microwave irradiation for 4.5 min using the following parameters: Discover mode; power, 200 W; ramp, 30 s; hold, 4.0 min; temperature, 100 °C; pressure, 12 bar; PowerMax-cooling mode. The reaction tube was allowed to cool to room temperature, and the reaction mixture was transferred into a round-bottom flask. The solvent was evaporated, citric acid (0.5 mL, 5%) was added, and the mixture was treated thrice with dichloromethane (15 mL). The combined extracts were dried over MgSO₄, and the solution was concentrated to 0.5 mL. Addition of Et₂O and hexane provided **9b, e, g–i, and k** as colorless solids.

2-Hydroxy-*N*-piperidin-1-yl-propionamide (9a). Colorless solid (63%); mp 78 °C (Et₂O–hexane); IR (KBr): 1667 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.44–1.50 (m, 2H), 1.68 (d, J = 6.87 Hz, 3H), 1.72–1.77 (m, 4H), 1.89–1.95 (m, 1H), 3.23 (t, J = 5.59 Hz, 4H), 4.78 (q, J = 6.87 Hz, 1H), 7.90 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 17.1, 23.2, 26.2, 53.0, 74.9, 172.1; Anal. Calcd for C₈H₁₆N₂O₂: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.70; H, 9.20; N, 16.35.

2-Cyclopropyl-2-hydroxy-*N*-piperidin-1-yl-acetamide (9b). Colorless solid (79%); mp 111 °C (Et₂O–hexane); IR (KBr): 1665 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.42–0.67 (m, 4H), 1.08–1.21 (m, 2H), 1.40–1.48 (m, 1H), 1.62–1.79 (m, 4H), 2.33 (s, 1H), 2.88–3.68 (m, 4H), 4.25 (d, J = 5.58 Hz, 1H), 7.63 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 0.6, 12.6, 20.9, 23.1, 55.0, 72.0, 174.5; Anal. Calcd for C₁₀H₁₈N₂O₂: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.53; H, 9.12; N, 14.10.

2-Cyclopropyl-2-hydroxy-*N*-morpholin-4-yl-acetamide (9c). Colorless solid (80%); mp 131 °C (Et₂O–hexane); IR (KBr): 1670 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.43–0.66 (m, 4H), 1.06–1.16 (m, 1H), 2.65 (s, 1H), 2.96–3.82 (m, 4H), 3.60–3.87 (m, 4H), 4.30 (d, J = 5.58 Hz, 1H), 7.64 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 1.7, 14.8, 55.0, 65.3, 73.4,

170.0; Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 13.99. Found: C, 53.78; H, 7.92; N, 13.90.

2-Cyclopentyl-2-hydroxyacetic Acid-*N'*-methyl-*N'*-phenylhydrazide (9d). Colorless solid (80%); mp 159 °C (Et₂O–hexane); IR (KBr): 1674 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.42–1.85 (m, 9H), 2.37–2.43 (m, 1H), 3.18 (s, 3H), 4.22 (d, *J* = 4.58 Hz, 1H), 6.84–7.28 (m, 5H), 8.06 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 26.1, 26.2, 26.7, 29.3, 41.3, 44.2, 74.4, 113.7, 120.5, 129.6, 140.5, 172.1; Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.67; H, 8.16; N, 11.17.

2-Hydroxy-*N*-morpholin-4-yl-2-(2-thienyl)-acetamide (9e). Yellow solid (67%); mp 160 °C (Et₂O–hexane); IR (KBr): 1673 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.07–3.12 (m, 4H), 3.40 (s, 1H), 3.64–3.88 (m, 4H), 5.72 (s, 1H), 6.95–7.31 (m, 3H), 8.26 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 55.9, 66.1, 67.0, 126.1, 126.8, 127.5, 143.1, 174.2; Anal. Calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56; S, 13.23. Found: C, 49.24; H, 5.90; N, 11.31; S, 13.18.

2-(2-Furyl)-2-hydroxy-*N*-morpholin-4-yl-acetamide (9f). Brown solid (67%); mp 134 °C (Et₂O–hexane); IR (KBr): 1668 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.03–3.29 (m, 5H), 3.63–3.87 (m, 4H), 5.65 (s, 1H), 6.35–7.43 (m, 2H), 7.27–7.41 (m, 1H), 7.84 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 56.1, 65.4, 67.8, 108.3, 111.2, 143.5, 153.2, 173.2; Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.99; H, 6.37; N, 12.26.

2-Hydroxy-2-naphth-1-yl-acetic Acid-*N'*,*N'*-dimethylhydrazide (9g). Colorless solid (78%); mp 161 °C (Et₂O–hexane); IR (KBr): 1670 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.44 (s, 1H), 2.63 (s, 6H), 5.62 (s, 1H), 7.40–7.64 (m, 5H), 7.80–7.88 (m, 2H), 8.11 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 47.5, 72.7, 124.2, 125.7, 126.1, 126.5, 127.2, 129.3, 130.2, 131.4, 134.6, 136.4, 171.2; Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.56; H, 6.72; N, 11.30.

2-Hydroxy-2-phenyl-acetic Acid-*N'*-methyl-*N'*-phenylhydrazide (9h). Colorless solid (66%); mp 82 °C (Et₂O–hexane); IR (KBr): 1672 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ

2.28 (s, 1H), 3.09 (s, 3H), 5.13 (s, 1H), 6.70–7.30 (m, 10H), 7.90 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 41.9, 74.1, 113.5, 122.0, 127.2, 127.9, 128.9, 130.0, 139.3, 149.4, 171.5; Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.52; H, 6.46; N, 10.95.

2-Hydroxy-2-phenyl-acetic Acid-*N'*,*N'*-dimethylhydrazide (9i). Colorless solid (63%); mp 93 °C (Et₂O–hexane); IR (KBr): 1667 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.50 (s, 1H), 2.60 (s, 6H), 5.44 (s, 1H), 7.27–7.41 (m, 5H), 8.10 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 47.7, 74.0, 127.2, 128.4, 129.3, 140.4, 170.5; Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.73; H, 7.29; N, 14.41.

2-Hydroxy-2-phenyl-*N*-piperidin-1-yl-acetamide (9j). Colorless solid (76%); mp 113 °C (Et₂O–hexane); IR (KBr): 1664 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.95–1.37 (m, 2H), 1.41–1.75 (m, 4H), 1.88–1.97 (m, 1H), 2.27–3.27 (m, 4H), 5.40 (s, 1H), 7.26–7.43 (m, 5H), 8.11 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 23.2, 25.3, 57.1, 72.3, 127.2, 128.0, 129.2, 140.5, 174.8; Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.33; H, 7.87; N, 12.10.

2-Hydroxy-*N*-morpholin-4-yl-phenyl-acetamide (9k). Colorless solid (75%); mp 140 °C (Et₂O–hexane); IR (KBr): 1670 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.65–3.26 (m, 5H), 3.62–3.86 (m, 4H), 5.40 (s, 1H), 7.26–7.44 (m, 5H), 8.21 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 56.0, 66.3, 72.2, 127.2, 128.2, 129.3, 140.3, 175.4; Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.94; H, 6.82; N, 11.85.

2-Hydroxy-*N*-piperidin-1-yl-acetamide (9l). Colorless solid (75%); mp 159 °C (Et₂O–hexane); IR (KBr): 1660 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.06–1.86 (m, 6H), 2.17–3.16 (m, 5H), 4.14–4.29 (m, 2H), 6.68 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 23.3, 25.9, 58.3, 60.6, 175.0; Anal. Calcd for $C_7H_{14}N_2O_2$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.00; H, 8.80; N, 17.60.

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