Conventional and Microwave-Assisted Conversion of Substituted 3-Amino-oxazolidin-2,4-diones into \( N',N' \)-Disubstituted \( \alpha \)-Hydroxyhydrazides

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Substituted 3-amino-oxazolidin-2,4-diones have been prepared by reacting cyanohydrins or \( \alpha \)-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 \( \alpha \)-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 \( \alpha \)-hydroxyhydrazides are \( \alpha \)-functionalized carboxylic acid hydrazide derivatives. Considerable research effort has been dedicated to the preparation of \( N',N' \)-disubstituted \( \alpha \)-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.\(^4\) 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 \( \alpha \)-hydroxyhydrazides. Their synthesis is

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\(^8\) Gotor, V.; Astorga, F.; Rebolloé, P. Synlett 1990, 387.


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 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. 

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 glycolonaltrile and commercially available mandelonitrile provided compounds 5j and 1 in only 29 (5j) and 47% (5l) yield, respectively. Therefore, we turned our attention to ethyl mandelate (6a) and ethyl glycode (6b) as starting materials. Their successive treatment with 1,1′-carbonyldi-(1,2,4-triazole) (CDT) and 1,1-disubstituted hydrazines afforded compounds 5h–l in higher yields of 50–69% (Scheme 2, Table 1).

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-hydroxy-carboxylic acid hydrazides and by reactions of 1,3,4-dioxazinan-2,5-diones

with hydrazines. 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.

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


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–1 into 9a–1 was accomplished in good yields of 63–80% within 45 min by refluxing compounds 5a–1 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 45 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-hydroxyster, 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-carbonyldimidazole (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 = 6.60 Hz, 4H), 3.80 (t, J = 6.60 Hz, 4H), 4.50 (d, J = 6.87 Hz, 1H), 7.49 (s, 1H); 13C NMR (100 MHz, CDCl3): δ 17.4, 51.4, 66.6, 67.9, 152.8, 156.9; Anal. Calcd for C10H15N3O3: C, 53.32; H, 6.95; N, 18.65. Found: C, 53.82, H, 6.85, 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 0.62–0.80 (m, 4H), 1.20–1.28 (m, 1H), 1.43–1.60 (m, 2H), 1.71–1.77 (m, 4H), 4.41 (d, J = 6.86 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 10.1, 23.3, 26.2, 50.2, 78.5, 152.9, 170.0; Anal. Calcd for C9H10N2O2: C, 55.54; H, 7.12; N, 14.31. 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 71 °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), 4.41 (d, J = 6.86 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 10.1, 23.3, 26.2, 50.2, 78.5, 152.9, 170.0; Anal. Calcd for C9H10N2O2: C, 55.54; H, 7.12; N, 14.31. Found: C, 54.69; H, 7.32; N, 14.31.

the reaction mixture was refluxed for 90 min. The organic layer
was subjected to microwave irradiation for an additional hour. Triethylamine (0.1 mL) was added, and the reaction mixture was transferred into a round-bottom flask. The solvent was evaporated, citric acid (0.5 mL) 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 EtO and hexane provided 9a−l as colorless solids.

Conventional-Assisted Synthesis of 9b, e, g−i, and k. 5b, 5d, 5e, 5f, 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 45 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) 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 EtO 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 (EtO−hexane); IR (KBrs): 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, 56.2, 50.3, 74.9, 172.1; Anal. Calcd for C15H21NO3C: 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 (EtO−hexane); IR (KBrs): 1665 cm−1; 1H NMR (400 MHz, CDCl3): δ 1.08−1.21 (m, 2H), 1.40−1.48 (m, 1H), 1.62−1.79 (m, 4H), 2.33 (s, 4H), 2.88−3.08 (m, 4H), 4.25 (d, J = 5.58 Hz, 1H), 6.93 (s, 1H); 13C NMR (100 MHz, CDCl3): δ 12.0, 21.9, 23.7, 55.0, 72.0, 174.5; Anal. Calcd for C15H21NO3C: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.70; H, 9.20; N, 16.35.

2-Cyclopropyl-2-hydroxy-N-morpholin-4-yl-acetamide (9c). Colorless solid (80%); mp 131 °C (EtO−hexane); IR (KBrs): 1665 cm−1; 1H NMR (400 MHz, CDCl3): δ 0.42−0.67 (m, 4H), 1.01−1.21 (m, 2H), 1.40−1.48 (m, 1H), 1.62−1.79 (m, 4H), 2.33 (s, 1H), 2.88−3.08 (m, 4H), 4.25 (d, J = 5.58 Hz, 1H), 7.84 (s, 1H); 13C NMR (100 MHz, CDCl3): δ 1.7, 14.8, 55.0, 65.3, 73.4.
2-Cyclopentyl-2-hydroxyacetic Acid-N-methyl-N-phenylhydrazone (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 C₁₀H₁₆N₂O₃: C, 57.72; H, 8.12; N, 11.28. Found: C, 57.67; 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 C₁₀H₁₆N₂O₄S: 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-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 C₁₀H₁₆N₂O₃: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.99; H, 6.37; N, 12.26.

2-Hydroxy-1-yl-acetic Acid-N,N-dimethyl-hydrazone (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 C₁₁H₁₆N₂O₂: 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,N'-methyl-phenylhydrazone (9h). Colorless solid (66%); mp 1672 °C (Et₂O–hexane); IR (KBr): 1672 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.88 (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, 130.3, 149.4, 171.5; Anal. Calcd for C₁₅H₁₆N₂O₃: 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'-dimethylhydrazone (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 C₁₅H₁₆N₂O₃: 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 C₁₅H₁₆N₂O₂: 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 C₁₅H₁₆N₂O₂: 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 C₁₅H₁₆N₂O₂: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.00; H, 8.80; N, 17.60.

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