

Synthesis of some hydroxamic acids Linked-natural amino acid

Marzough Aziz DagerAlbalawi^{1*}

¹Department of Chemistry, University college- Alwajh, University of Tabuk, Saudi Arabia

Abstract: A series of amino acid derivative hydroxamic acid have been synthesized as promising compounds for further biological activity. These compounds were fully characterized by spectroscopic techniques including; ¹H, ¹³C, DEPT 135 and HRMS.

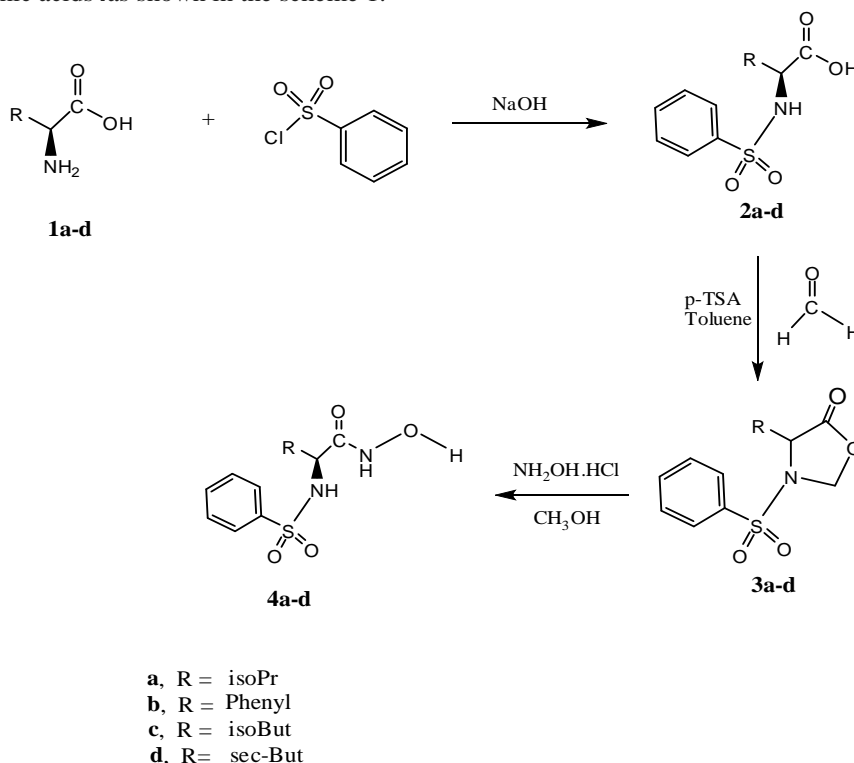
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I. Introduction

Since their discovery by Wahlroos and Virtanen (1) in 1959, and over the past decades, the chemistry and biochemistry of hydroxamic acids and their derivatives have attracted considerable attention, due to their pharmacological, toxicological and pathological properties. Recently, the compounds containing hydroxamic acid functionality, have been reported to exhibit multifarious pharmacological effects including antioxidant, [1], anticancer, [2,3], antibacterial agents, [4], antifungal, [5], growth factors, [6], anti-melanogenic, [7], antimalarial, [8], enzyme inhibitors, [9], rare earth mineral collectors, [10], and reagents for solvent extraction and spectrophotometric determination of metals, [11]. A number of hydroxamic acid derivatives have also been found to inhibit several important enzymes in cellular systems, including FeII and MnII E. coli methionine aminopeptidase, [12], γ -lactum based histone deacetylase (HDACs), [13], and matrix metalloproteinases, [14, 15]. In view of the above applications, the present work relates to the synthesis and characterization of new hydroxamic acids.

II. Results And Discussion

In present investigation the synthetic approach was achieved in three steps as shown in Scheme-1. Initially commercially available amino acid **1** has been protected with phenylsulfonyl chloride in the presence of one equivalent of sodium hydroxide to afford compound **2**. Compound **2**, when subjected to condensation with paraformaldehyde and para toluene sulfonic acid as catalyst gave the corresponding 1,3-oxazolidin-5-ones **3**. The cleavage of the latter with the hydroxylamine hydrochloride in methanol led to the N-phenylsulfonyl-2-amino hydroxamic acids **4** as shown in the scheme 1.



scheme 1: Synthetic route for the synthesis of hydroxamic acids **a-d**

In each step, progress of the reaction was monitored by TLC (Thin layer chromatography). The ^1H NMR spectra of hydroxamic acids under investigation show the characteristic singlet of the proton of the hydroxyl group in the region 11-11.5 ppm. A broad signal in the region 7.2-8.22 ppm which evidently belonged to the Ar-H and NH protons of the hydroxylamine unit. The ^{13}C -NMR spectra exhibit absorption signal due to carbonyl, C=O carbon nearby 165 ppm. The chemical shifts of aromatic carbon appear in the region 124-138 ppm. Beside these signals, a singlet near 21 ppm and a singlet at 171 ppm appeared which correspond to the carbon atom of alkyl group and carboxy group respectively. DEPT 135 spectrum indicates that the methylene carbon appears at 24.45, 25.28 and 37.24, CH carbons are noticed in the region between 127.7 ppm to 134.8 ppm.

III. Experimental

All reactions were performed under an argon atmosphere and were monitored by thin-layer chromatography (TLC) Merck 60 F-254 silica-gel plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (70–230 mesh) using ethyl acetate and cyclohexane mixture as eluents. Melting temperatures were determined on an Electrothermal 9002 apparatus and were reported uncorrected. NMR spectra were recorded on a Bruker AC-300 spectrometer at 300 MHz (^1H) and 75 MHz (^{13}C). All chemical shifts were reported as δ values (ppm) relative to internal tetramethylsilane. High-resolution mass spectra (HRMS) were recorded on a matrix-assisted laser desorption-ionization time-of-flight (MALDI-TOF) Perspective Biosystems Voyager DE-STR instrument.

Synthesis:

General procedure for synthesis of sulfonamide protected acids:

The starting materials **2a-d** were prepared according to [16].

N-phenylsulfonyl-L-valine (2a). Prepared from commercial L-valine and p-toluenesulfonyl chloride. Crystallization from ether afforded the product as a white solid (yield 80%); ^1H NMR (300 MHz, methanol-*d*₄) δ 0.90 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 2.21 (m, 1H), 3.54 (d, *J* = 7.5 Hz, 1H), 7.62-7.78 (m, 7H).

N-phenylsulfonyl-L-phenylalanine (2b). Prepared from L-phenylalanine; ^1H NMR (300 MHz, methanol-*d*₄) δ 3.22 (d, *J* = 14.7, 2H), 4.87 (t, 1H), 7.32-7.98 (m, 11H), 11.51 (s, 1H).

N-phenylsulfonyl-L-leucine (2c). Prepared from commercial L-isoleucine; ^1H NMR (300 MHz, methanol-*d*₄) δ 0.86 (d, *J* = 6.4 Hz, 6H), 1.68 (m, 1H), 2.16 (t, 2H), 3.81 (m, 1H), 7.61-7.87 (m, 6H), 11.55 (s, 1H).

N-phenylsulfonyl-L-isoleucine (2d). Prepared from L-leucine; ^1H NMR (300 MHz, methanol-*d*₄) δ 0.85 (m, 6H), 1.32 (q, 2H), 1.83 (m, 1H), 3.77 (d, *J* = 9.2, 1H), 7.61-7.88 (m, 6H), 11.58 (s, 1H).

General procedure for synthesis of substituted 1,3-oxazolidin-5-ones:

The reactions were performed according to the literature [17]. The synthesis of substituted 1,3-oxazolidin-5-ones by stirring suspension of sulfonamides **2a-d**, toluene, paraformaldehyde and para-toluene sulfonic acid as catalyst. It was reported that the reaction was completed at room temperature in a short duration of time with good yield of oxazolidin-5-one.

Synthesis of product 4-isopropyl-3-(phenylsulfonyl)oxazolidin-5-one 3a: The mixture of compound **2a**, paraformaldehyde, Toluene and para-toluene sulfonic acid as catalyst afforded the compound **3a**. Yield: 65%. ^1H NMR (300 MHz, CDCl_3) δ : 0.98 (d, 6H), 2.00 (q, 1H), 3.62 (dd, *J* = 14.8, 1H), 7.42-7.9 (m, 7H). ^{13}C NMR (75 MHz, CDCl_3) δ : 18.42, 18.46, 31.04, 62.76 (C-N), 94.11 (CH₂-O), 127.28-136.00 (6 C aromatic), 171.19 (CO).

Synthesis of product 4-benzyl-3-(phenylsulfonyl)oxazolidin-5-one 3b:

The compound **3b** was prepared as the same procedure as **3a** which was obtained as white solid. Yield: 70%. ^1H NMR (300 MHz, CDCl_3) δ : 3.31 (d, 2H, *J* = 5.6), 4.45 (t, 1H), 5.65 (dd, *J* = 9.2, 2H), 7.22-7.94 (m, 10H). ^{13}C NMR (75 MHz, CDCl_3) δ : 37.24, 58.54, 79.83 (CH₂-O), 127.49-136.13 (12 C aromatic), 171.39 (CO); DEPT 135: (300 MHz, CDCl_3) δ :

Synthesis of product 4-isobutyl-3-(phenylsulfonyl)oxazolidin-5-one 3c:

White solid. Yield: 80%. ^1H NMR (300 MHz, CDCl_3) δ : 0.93 (m, 6H, 2CH₃), 1.71 (m, 1H), 2.00 (m, 1H), 4.45 (t, 1H), 5.31 (d, *J* = 14.6, 1H), 5.7 (d, *J* = 14.4, 1H), 7.61-7.92 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 21.43, 22.75, 24.45, 38.44, 56.20, 78.76 (CH₂-O), 127.64-135.98 (6 C aromatic), 172.249 (CO).

Synthesis of product 4-sec-butyl-3-(phenylsulfonyl)oxazolidin-5-one 3d:

White solid: Yield 54%. ^1H NMR (300 MHz, CDCl_3) δ : 1 (m, 6H, 2CH₃), 1.44 (m, 2H), 2.22 (m, 1H), 4.46 (d, *J* = 14.6, 1H), 5.32 (d, *J* = 14.6, 1H), 5.6 (d, *J* = 14.6, 1H), 7.61-7.95 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 11.46, 14.93, 25.28, 37.75, 61.76, 79.56 (CH₂-O), 127.63-135.95 (6 C aromatic), 171.03 (CO).

General procedure for the synthesis of Hydroxamic acid:

Synthesis of product (S)-N-hydroxy-3-methyl-2-(phenylsulfonamido)butanamide4a: White solid; m.p. 119–121 °C; Yield 62.5%. ¹H-NMR (CDCl₃) δ: 0.8 (m, 6H, 2CH₃), 2 (m, 1H), 7.43-8.22 (m, 7H); 11.3 (s, 1H, OH); ¹³C-NMR(CDCl₃) δ: 16.71, 17.48, 31.37, 61.12(2 C), 127.21(2 C), 127.28, 132.75, 139.38, 171.09(CO). DEPT 135 δ: 18.42, 18.46, 31.4, 62.76, 127.64, 128.21, 128.93, 129.89, 134.31. (MALDI-TOF) calculated for C₁₅H₁₆N₂O₄S[M]⁺ : C₁₁H₁₆N₂O₄S [M]⁺ : 272.08308 Found: 272.08221

Synthesis of product (S)-N-hydroxy-3-phenyl-2-(phenylsulfonamido)propanamide4b:

NMR ¹H: (300 MHz, CDCl₃) δ: 3.25(dd, J=14.8, J=5.6 Hz, 2H), 4.13 (t, 1H), 7.20- 8.16 (m, 12H), 11.35 (s, 1H, OH). ¹³C: (75MHz, CDCl₃) δ: 37.30(CH₂), 57.23, 126.81-138.16 (12 C aromatic), 171.40(CO). DEPT 135 δ: 37.24(CH₂), 58.54, 127.49, 127.73, 128.83, 129.89, 129.94, 134.26. HRMS (MALDI-TOF) calculated for C₁₅H₁₆N₂O₄S[M]⁺ : 320.08307 Found: 305.08162.

Synthesis of product (S)-N-hydroxy-4-methyl-2-(phenylsulfonamido)pentanamide4c:

A yellowish solid, m.p: 153–156 °C; Yield 61.8%; ¹H NMR (300 MHz, CDCl₃) δ: 0.98 (d, 6H, 2CH₃), 1.5 (m, 1H), 1.89 (m, 1H), 3.88 (t, 1H), 7.56 - 8.22 (m, 7H), 11.16 (s, 1H, OH); ¹³C: (75MHz, CDCl₃) δ: 21.45, 21.98, 24.45, 38.44, 56.20, 124.70-128.9 (5C), 173.12(CO). DEPT 135 δ: 21.43, 22.75, 24.45(CH₂), 38.44, 56.20, 127.46, 128.21, 129.9, 134.36. HRMS (MALDI-TOF) calculated for C₁₂H₁₈N₂O₄S[M]⁺ : 286.09761 Found: 286.09218.

Synthesis of product (2S)-N-hydroxy-3-methyl-2-(phenylsulfonamido)pentanamide4d: White solid; m.p: 161-164 °C. Yield 54%. NMR ¹H: (300 MHz, CDCl₃) δ: 0.93 (d, 6H, 2CH₃), 1.55 (m, 2H), 2.12 (m, 1H), 3.78 (d, J = 14.5, 1H), 7.61- 8.11 (m, 5H). ¹³C: (75MHz, CDCl₃) δ: 11.78, 14.16, 26.4, 34.28, 62.3, 125.21-138.8 (C aromatic), 172.82(CO). DEPT 135 δ: 11.46, 14.83, 25.28 (CH₂), 37.75, 127.63, 129.89, 134.3. HRMS (MALDI-TOF) calculated for C₁₂H₁₈N₂O₄S[M]⁺ : 286.09872 Found: 286.09213.

IV. Conclusion

We have developed a facile method to synthesize different amino acid derived Hydroxamic acid. The reaction offers convenience, mild conditions and good to excellent yields. Evaluation of this product in biological activity is in progress.

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