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ORIGINAL PAPER

Synthesis and Crystal Structure Analysis of Methyl 2-Hydroxyimino-3-phenyl-propionate

Xiao-liu Li · Xiao-li Zhen · Jian-rong Han · Shouxin Liu

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Abstract As precursors of α-amino acids, methyl 2-hydroxyimino-3-phenyl-propionate (F.W. 193.20) was synthesized, characterized by ^{1}H NMR, IR, element analysis and confirmed by X-ray crystal structure analysis. This compound crystallizes in monoclinic class under the space group $P2_1/c$ with cell parameters, $a = 8.6435(17)$ Å, $b = 5.4957(11)$ Å, $c = 21.146(4)$ Å; $\beta = 97.12(3)°$, and $Z = 4$. The structure exhibits inter-molecular hydrogen bonds of the type O–H···N, O–H···O, C–H···O.

Keywords α-Oximino ester · Nitrosation · Oximation · Synthesis · Crystal structure · Hydrogen bond

Introduction

Natural amino acids and peptides are particularly interesting natural leads due to their potent biological activities. However, unnatural α-amino acids have also acquired great importance in medicinal chemistry, therefore the synthesis of unnatural α-amino acids have attracted intense interest. α-Oximino acidic esters are particularly useful precursors of α-amino acids. The catalytic hydrogenation of α-oximino acids or esters affords a convenient method for the synthesis of α-amino acids. Miller et al. [1] reported synthesis of α-amino acids by reduction of α-oximino acidic esters with titanium(III) chloride and sodium borohydride. α-Oximino acidic esters as precursors of α-amino acid are readily available either by reaction of hydroxylamines with α-keto acid derivatives or by nitrosation of diethyl malonate [2]. In addition, α-oximino acidic esters have been utilized in various ways for the preparation of nitro compounds [3] and chloro nitroso compounds [4]. Thus, study on synthetic methods of α-oximino acidic esters is very important. Generally, α-oximino acids or esters [5] may be prepared from (a) α-keto acids or esters [6]; (b) α-halogen acids or esters [7, 8]; (c) substituted acetoacetic [9] or malonic esters [10] and (d) substituted malonic acids [11]. In the present work, we wish to report the synthesis of methyl 2-hydroxyimino-3-phenyl-propionate by nitrosation oximation of substituted malonic esters (Scheme 1). It is characterized by ^{1}H NMR, IR and element analysis, and the ester's crystal structure was determined by X-ray diffraction analyses.

X. Li (✉) · X. Zhen
College of Chemistry and Environmental Science,
Hebei University, 071002 Baoding, People's Republic of China
e-mail: lixl@hbu.edu.cn

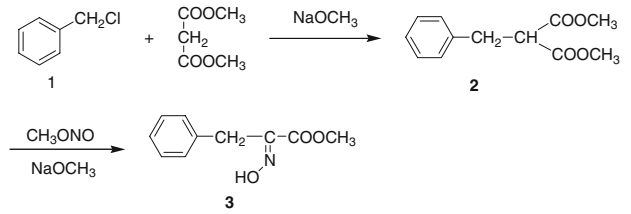
X. Zhen · J. Han
College of Sciences, Hebei University of Science and Technology, 050018 Shijiazhuang,
People's Republic of China

S. Liu (✉)
College of Chemical and Pharmaceutical Engineering,
Hebei University of Science and Technology,
050018 Shijiazhuang, People's Republic of China
e-mail: chlsx@263.net

Experimental

General. Melting points, measured with an Xt-4 apparatus, are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE II500 instrument in $CDCl_3$ solution, using tetramethylsilane as an internal reference. Elemental analyses were performed on a Perkin-Elmer 2400C instrument. Infrared spectra were recorded on PE-1730 instruments.

Starting material benzyl chloride **1** was commercially available and used without further purification. All chemicals were reagent grade and were used without further



Scheme 1 Route of synthesis of **3**

purification, unless noted otherwise. The solvent ethanol was refluxed over sodium turnings and then distilled fractionally.

The Preparation of Substituted Dimethyl Malonate **2**

Metal sodium (4.6 g, 0.2 mol) were added to a 250 ml reaction flask, which was fitted with magnetic stirrer, reflux condenser, thermometer and dropping funnel. Then anhydrous ethanol (100 ml) was slowly added dropwise under magnetic stirrer until metal sodium was entirely dissolved. After cooling the solution to 50 °C, dimethyl malonate (0.2 mol) was added dropwise to above solution at 50 °C. The mixture was stirred magnetically for 10 min, then benzyl chloride **1** (0.205 mmol) was added to the reaction solution, and the mixture was heated to reflux for 4 h. The solvent was removed in vacuo. The residue obtained was added to equal volume mixture of water and ice, and the organic layer was separated. Water layer was extracted with ethyl acetate (4 × 30 ml) and united with organic layer and dried over $MgSO_4$. The solution was condensed under reduced pressure to obtain the crude product **2**, which could be used directly next reaction without purification.

Synthesis of Methyl 2-Hydroxyimino-3-Phenyl-Propionate

2 (0.1 mol) were added to a 250 ml reaction flask, which was fitted with mechanical stirrer, refluxing condenser having a drying tube and dropping funnel. After cooling to −20 °C with liquid nitrogen, methyl nitrite (0.105 mol) was added. Then CH_3ONa solution (0.1 mol) was slowly added dropwise under mechanical stirrer. The mixture was placed in refrigeratory for 12 h. The solvents were removed in vacuo, the residue obtained was added to equal volume mixture of water. The mixture was controlled pH = 6 with dilution hydrochloric acid, which extracted with ethyl acetate (4 × 50 ml) and combined organic layer and dried over anhydrous Na_2SO_4. The solution was condensed under reduced pressure, followed by column chromatography over silica gel (AcOEt/hexane, 1:1) gave colorless solid **3** in 92% yield. m.p. 74–76 °C ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 3.83(s,3H), 3.99(s,2H),7.20–7.32 (m,5H), 9.64 (s,1H); IR (KBr) ν 3,227, 1,742, 1,650, 1,600, 1,495 cm^{-1}; Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.29; H, 5.65; N, 7.33.

X-Ray Crystallography

Crystals of the Oximino Ester suitable for X-ray diffraction analysis were obtained by slow evaporation from ethyl acetate after 7 days at room temperature. The data were collected with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved using direct methods and refined by full-matrix least-squares techniques. All non-hydrogen atoms were assigned anisotropic displacement parameters in the refinement. All hydrogen atoms were added at calculated positions and refined using a riding model. The structures were refined on F^2 using SHELXTL-97 [12]. The crystals used for the diffraction study showed no decomposition during data collection. The final R values (on F^2) were 0.0404 of the title compound. The crystal data and some details of the structure determination are summarized in Table 1. The selected bond lengths and bond angles are given in Table 2.

Table 1 Crystallographic data and structure refinement for complex **3**

Empirical formula	$C_{10}H_{11}NO_3$
Formula weight	193.20
Temperature (K)	113(2)
Wavelength (Å)	0.71073
Crystal system, space group	Monoclinic, $P2(1)/n$
Unit cell dimensions	a = 8.6435(17) Å, b = 5.4957(11) Å, c = 21.146(4) Å; β = 97.12(3)°
Volume (Å^3)	996.7(3)
Z, calculated density (g cm^{-3})	4, 1.287
Absorption coefficient (mm^{-1})	0.096
$F_{(000)}$	408
Crystal size (mm^{-3})	0.18 × 0.16 × 0.12
Range for data collection	1.94–25.02°
Limiting indices	$-9 \le h \le 10$, $-6 \le k \le 6$, $-25 \le l \le 25$
Reflections collected/unique	6,972/1,763 [R_{int} = 0.0357]
Completeness to Θ = 25.01	99.7%
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.068
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0404, wR_2 = 0.1005
R indices (all data)	R_1 = 0.0503, wR_2 = 0.1075
Extinction coefficient	0.051(7)
Largest diff. peak and hole	0.163 and −0.194 e Å^{-3}

Table 2 Selected bond lengths (Å) and angles (°) for **3**

O(1)–C(9)	1.220 (2)	C(9)–O(1)–C(10′)	110.6 (4)
O(1)–C(10′)	1.494 (6)	C(8)–N(1)–O(3)	113.65 (13)
O(2)–C(9)	1.321 (2)	N(1)–C(8)–C(7)	126.75 (15)
O(2)–C(10)	1.450 (2)	N(1)–C(8)–C(9)	114.51 (15)
O(3)–N(1)	1.3956 (16)	C(7)–C(8)–C(9)	118.72 (15)
O(3)–H(3)	0.8200	O(1)–C(9)–O(2)	124.39 (16)
N(1)–C(8)	1.285 (2)	O(1)–C(9)–C(8)	121.29 (16)
		O(2)–C(9)–C(8)	114.33 (16)

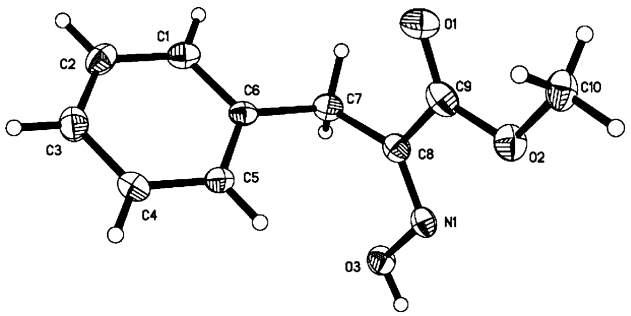


Fig. 1 The molecular structures of **3**, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level

Table 3 Hydrogen bonded geometry, distances and angles are given in (Å) and (°)

No.	D–H···A	d(D–H)	d(H···A)	d(D···A)	θ(D–H···A)	Symmetry code
1	O3–H3···N1	0.820	2.118	2.769	136.2	1−*x*, −*y*,−*z*
2	O3–H3···O2	0.820	2.582	3.356	158.0	1−*x*, −*y*,−*z*
3	O3–H3···O3	0.820	2.98	3.359	111.0	1−*x*, −*y*,−*z*

D donor, *A* acceptor

Results and Discussion

The crystal structure of **3** is illustrated in Fig. 1. It is composed of a phenyl ring moiety, a oxime group and a ester group, eight atoms O1, O2, O3, N1, C7, C8, C9, C10 display an almost coplanar configuration and with a mean deviation to the least square plane 0.0166 Å, and it is almost vertical with aromatic ring C1–C6, their dihedral angle is 84.4(6)°.

Intermolecular hydrogen bond of the type O–H···N O–H···O, and C–H···O are found in the crystal structure of **3** (seen in Table 3). Atom N1, O2, O3 acts as a hydrogen-bond donor respectively, via atom H3–O3 to generate the supramolecular structures. They are O3–H3···N1 (2.769 Å, 136.2°), O3–H3···O2 (3.356, 158°), O3–H3···O3 (3.359, 111°) with symmetry code $1-x, -y, -z$. Furthermore, the structures of α-oximino acidic esters are linked layer by layer, in which up and down are connect by bifurcated hydrogen bonds of C5–H5···O1 (symmetry code: $x, -1+y, z$), C7–H7···O3 (symmetry code: $x, 1+y, z$) and C10–H10···O1 (symmetry code: $-1+x, y, z$). The hydrogen bonds make the molecules form a column along *a*-axis, When viewed along the *a*-axis, the molecules are interlinked by hydrogen bonds as shown in Fig. 2.

Supplementary Material

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-696915. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail:deposit@ccdc.cam.ac.uk).

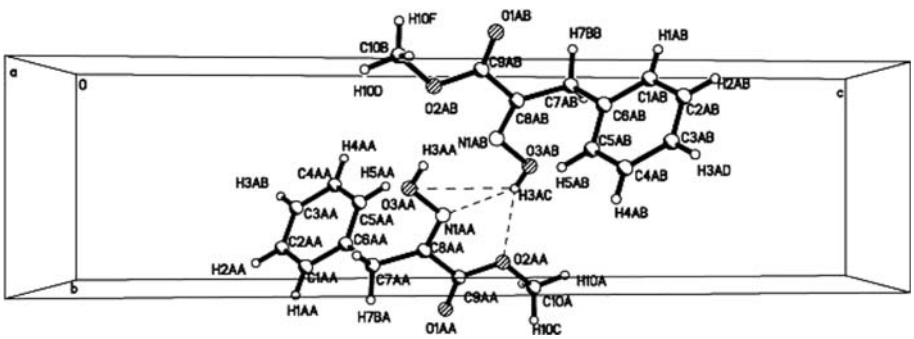


Fig. 2 The hydrogen bond system between molecular **3**, The *dashed lines* represent the intermolecular hydrogen bonds (H-bonds are drawn between donor and acceptor atoms)

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