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Improved Synthesis and Crystallographic Analysis of (*E*)-Ethyl 2-(Hydroxyimino)-3-(4-methoxyphenyl)-3-oxopropanoate and *erythro*-*N*-Acetyl-β-(4-methoxyphenyl)serine Ethyl Ester

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(*E*)-Ethyl 2-(hydroxyimino)-3-(4-methoxyphenyl)-3-oxopropanoate has been synthesized by the oximation of ethyl 3-(4-methoxyphenyl)-3-oxopropanoate with ethyl nitrite in the presence of multi-pore activated-K_2CO_3. A one-pot procedure has also been developed for the conversion of this oxime to the corresponding *erythro*-2-acetamido-3-hydroxy-3-(4-methoxyphenyl)propionic ethyl ester. Their configurations were unambiguously confirmed by X-ray crystallographic determination. The oxime crystallized as a monoclinic system with space group P21/c and the following cell parameters: a = 11.524(3) Å, b = 7.2367(16) Å, c = 14.866(4) Å, β = 111.027(4) and Z = 4, whereas the *erythro*-*N*-acetyl-β-(4-methoxyphenyl)serine ethyl ester crystallized as a triclinic system with space group P-1 and the following cell parameters: a = 7.6451(6) Å, b = 13.3326(10) Å, c = 16.2679(13) Å, α = 67.314(7), β = 79.917(7), γ = 88.516(7) and Z = 2. The crystal packing in both of these structures was stabilized by intermolecular O-H---O and C-H---O hydrogen bonds.

Keywords: Oximation, Asymmetric reduction, Amino acid, Crystal structure, Hydrogen bond.

INTRODUCTION

The preparation of oxime esters and subsequently reduction is a very important route for synthesizing of amino acids [1-6]. Traditionally, the oximation reaction of β-dicarbonyl compounds was carried out with sodium nitrite in acetic acid or with nitrous esters in strong alkaline conditions. However, the former method was only limited to the oximation of non-substituted β-dicarbonyl compounds. Although the latter method could be widely applied to mono- and non-substituted β-dicarbonyl compounds, some drawbacks are still obvious in practical application. (1) Sodium ethoxide is a strong base and has corrosion to equipments. (2) low boiling point and the hazard of ethyl nitrite result to that the process is not green and inconvenient. In order to avoid these disadvantages, we developed a novel base multi-pore K_2CO_3 with higher activity compared to normal K_2CO_3 to replace sodium ethoxide to execute the oximation. β-(4-Methoxyphenyl)serine, as the unnatural amino acid, can be found in numerous naturally occurring biological products [7,8]. In this paper, we report the preparation of ethyl 3-(4-methoxyphenyl)-3-oxopropanoate *via* directly leading ethyl nitrite to the reaction solution using multi-pore activated-K_2CO_3. Subsequently, we develop a one-pot method of the oxime converted to *erythro*-*N*-acetyl-β-(4-methoxyphenyl)serine ethyl ester which can afford optical β-(4-methoxyphenyl)serine by enzymatic resolution [9]. Meanwhile, the two crystal structures of (*E*)-ethyl 2-(hydroxyimino)-3-(4-methoxyphenyl)-3-oxopropanoate and *erythro*-*N*-acetyl-β-(4-methoxyphenyl)serine ethyl ester will be reported.

EXPERIMENTAL

All of the reagents used in the current study were used as supplied without prior purification. Melting points were measured on an Xt-4 apparatus using an uncorrected thermometer. ^{1}H NMR spectra were recorded on a Bruker AVANCE II500 instrument in $CDCl_3$ using tetramethylsilane as an internal reference. Infrared spectra were recorded on a PE-1730 spectrometer. LC-MS was performed on a Thermo Finnigan LCQ-Advantage mass spectrometer. Multi-pore activited K_2CO_3 was prepared using an LGJ-10 vacuum freeze dryer.

Synthesis

Preparation of multi-pore activated-K_2CO_3: The crystalline potassium carbonate (200 g) was frozen at -50 °C using a vacuum freeze dryer. Subsequent vacuum sublimation and drying over 24 h gave multi-pore activated-K_2CO_3.

(E)-Ethyl 2-(hydroxyimino)-3-(4-methoxyphenyl)-3-oxopropanoate (2): A solution of sulfuric acid (7.5 g, 0.075

mol) in a mixture of water (100 mL) and ethanol (5 mL) was added to a stirred solution of sodium nitrite (10.4 g, 0.15 mol) in a mixture of water (50 mL) and ethanol (7 mL) in a dropwise manner, resulting in the formation of ethyl nitrite. The ethyl nitrite gas was bubbled through a stirred mixture of multi-pore activated-K_2CO_3 (41.7 g, 0.3 mol) and ethyl 3-(4-methoxy-phenyl)-3-oxopropanoate (22.3 g, 0.1 mol) in ethanol (100 mL) at 10 °C for 5 h. The reaction mixture was then filtered to remove any solids and the resulting filtrate was collected and distilled to dryness *in vacuo*. The resulting residue was dissolved in cold water (50 mL) and the pH of the solution was adjusted to 5 using a 0.5 M solution of HCl. The solution was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was then removed *in vacuo* to give the desired product **2** as a solid. (17.8 g, 71 %). m.p.: 112-114 °C. IR (KBr, ν_{max}, cm^{-1}): 3402, 1696, 1666, 1595. ^1H NMR ($CDCl_3$, 500 MHz): δ 9.52 (br, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.31 (q, *J* = 7.0 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 188.4, 165.1, 160.9, 149.8, 131.9, 127.5, 114.5, 62.7, 55.8, 29.8, 14.0. Crystals of the oximino ester **2** suitable for X-ray diffraction analysis were obtained by slow evaporation over a period of 5 days from a dichloromethane/*n*-hexane mixture.

***erythro*-Ethyl-2-acetamido-3-hydroxy-3-(4-methoxy-phenyl) propanoate (3):** A solution of **2** (12.6 g, 50 mmol) in ethanol (91 mL) and acetic acid (3 mL) was treated with 10 % Pd/C (1 g) and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen for 24 h. The pH of the reaction was adjusted to 7 by the addition of a 2 M solution of NaOH and the resulting mixture was treated with acetic anhydride (15 g, 147 mmol). The reaction mixture was stirred at room temperature overnight and then filtered. The filtrate was collected and concentrated *in vacuo* to give a residue, which was suspended in water. The mixture was then filtered to give the desired *erythro*-product **3** as a white solid (12.1 g, 86 %). m.p.: 146-148 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.15 (dd, *J* = 2.0, 7.0 Hz, 2H), 6.85 (dd, *J* = 2.0, 7.0 Hz, 2H), 6.25(d, *J* = 7.0 Hz, 1H), 5.22 (dd, *J* = 3.5, 5.5 Hz, 1H), 4.96 (dd, *J* = 3.5, 6.5 Hz, 1H), 4.44 (d, *J* = 5.5 Hz, 1H), 4.20 (q, *J* = 7.5 Hz, 2H), 2.04 (s, 3H), 1.27 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.7, 169.5, 159.4, 131.2, 127.1, 113.7, 74.9, 62.0, 59.3, 55.2, 22.9, 14.1. HRMS: calcd for $C_{14}H_{20}NO_5$ $[M + H]^+$ 282.1341; found 282.1329. Crystals of the *erythro*-product **5** suitable for X-ray diffraction analysis were obtained by slow evaporation from ethyl acetate over a period of 3 days at room temperature.

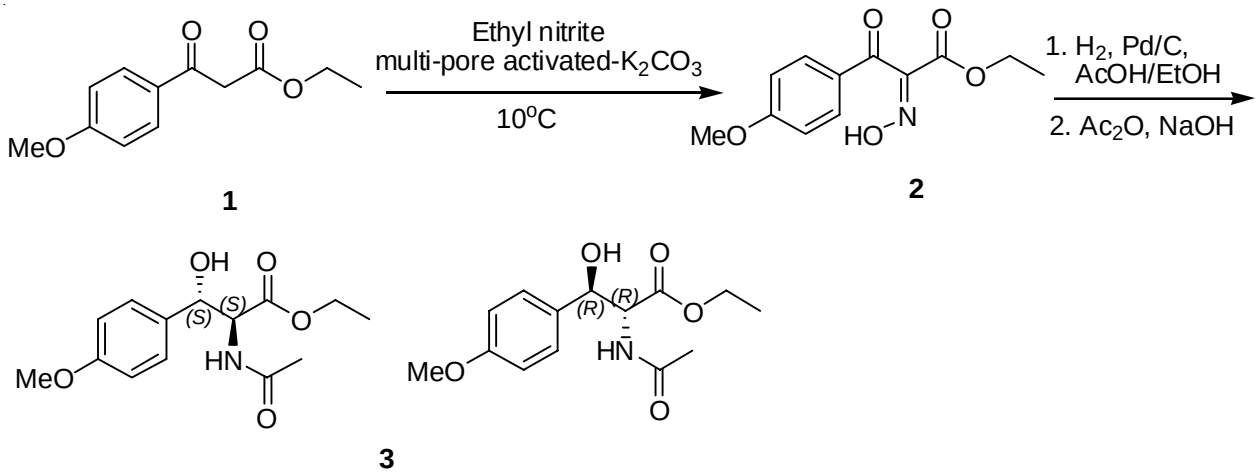
X-ray crystallography: Data for single crystals of oxime **2** and *erythry*-**3** were collected on a standard Rigaku Saturn 724 CCD Area Detector System and an Agilent SuperNova (Dual, Cu at zero, Eos) diffractometer equipped with a normal-focus molybdenum-target X-ray tube (λ = 0.71073 Å), respectively. The structures were 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 [10]. The crystals used for the diffraction study showed no decomposition during data collection. The final R values (on F^2) were 0.032 for oxime **2** and 0.065 for *erythry*-**3**. Crystal data and some details of the structural determination are summarized in Table-1.

TABLE-1
CRYSTAL DATA AND STRUCTURAL REFINEMENTS FOR COMPOUND **2** AND **3**

Parameter	Compound **2**	Compound **3**
Empirical formula	$C_{12}H_{13}NO_5$	$C_{14}H_{19}NO_5$
Formula weight	251.23	562.60
Temperature (K)	113(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system, space group	Monoclinic, P2(1)/c	Triclinic, P -1
	a = 11.524(3) Å,	a = 7.6451(6) Å,
	b = 7.2367(16) Å,	b = 13.3326(10) Å,
	c = 14.866(4) Å	c = 16.2679(13) Å
	β =111.027(4) °	α = 67.314(7)°
		β = 79.917(7)°
		γ = 88.516(7)°
Volume ($Å^3$)	1157.2(5)	1504.7(2)
Z, Calculated density ($g\ cm^{-3}$)	4, 1.442	2, 1.242
Absorption coefficient (mm^{-1})	0.113	0.094
F(000)	528	600
Crystal size (mm^{-3})	0.30 × 0.22 × 0.14	0.48 × 0.41 × 0.35
Range for data collection	1.89-27.87°	3.048 - 26.022°
Limiting indices	-15<=h<=14,	-9<=h<=9,
	-8<=k<=9,	-16<=k<=16,
	-19<=l<=19	-19<=l<=20
Reflections collected/unique	11640 / 2761	10656 / 5934
	[R(int) = 0.0403]	[R(int) = 0.0317]
Completeness to θ = 31.11	100.0 %	99.8 %
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.059	1.041
Final R indices [I > 2σ(I)]	R1 = 0.0321	R1 = 0.0645
	wR2 = 0.0789	wR2 = 0.1680
R indices (all data)	R1 = 0.0435	R1 = 0.0935
	wR2 = 0.0818	wR2 = 0.1938

RESULTS AND DISCUSSION

Our improved approach for the synthesis of (±)-*erythro*-**3** is shown in **Scheme-I**. Initial attempts to use commercial anhydrous K_2CO_3 to allow for the oximation of **1** with ethyl nitrite were unsuccessful because of the poor activity of this K_2CO_3 material. The preparation of multi-pore-K_2CO_3 using a vacuum freeze drier was developed by us. The loss of crystal water of crystalline potassium carbonate produced multi-pore structure. Multi-pore-K_2CO_3 exhibits stronger alkalinity to normal anhydrous K_2CO_3 because of its larger specific surface area. As expected, intermediate (*E*)-oxime **2** was successfully synthesized from compound **1** in the presence of multi-pore-K_2CO_3. The *trans* configuration of oxime **2** was unambiguously confirmed by X-ray crystallography. A convenient one-pot approach was developed for the step-wise conversion of compound **2** to *erythro*-**3** The first step in this one-pot process involved the diastereoselective catalytic hydrogenation of oxime **2** over Pd/C in a mixture of methanol and acetic acid to give ethyl *erythro*-β-(4-methoxyphenylalanine)serine ethyl ester, which was subsequently *N*-acetylated in the presence of Ac_2O and NaOAc. Compared with previously published methods [9,11], the weakly acidic solvent system used for the



Scheme-I: Synthesis of (±)-*erythro*-*N*-acetyl-β-(4-methoxyphenyl)serine ethyl ester **3**

hydrogenation in the current approach (*i.e.*, AcOH/MeOH) performed as a suitable replacement for absolute ethanolic HC1 or concentrated HCl/MeOH. Furthermore, this method provided a high yield of the product following a simple workup procedure. According to the mechanism proposed by Chang and Hartung [11], the polar oxygen and nitrogen atoms of the substrate molecule would be adsorbed onto the surface of the Pd catalyst to form a rigid ring-like structure, which would undergo the hydrogenation reaction to give the *erythro*-steric structure exclusively. The configuration of *erythro*-**3** was unambiguously confirmed by X-ray crystallography.

Crystal structure of oxime 2: The crystal structure of oxime **2** is shown in Fig. 1. The structure is composed of one aromatic ring moiety and one oximino ester side chain. The side chain oximino ester (O5, N1, C9, C10, O3, O4, C11) and the aromatic ring (C2-C9, O2) displayed a coplanar arrangement with mean deviation values to the least square plane of 0.0303 and 0.0353 Å, respectively. The dihedral angle between the two planes was 96.8(2)°. When viewed along the C8-C9 bond, the molecules displayed a staggered conformation with C5 opposite to O2 and C10 opposite to N1. When viewed along the C5-C8 or C9-C10 bond, the molecules adopted an almost eclipsed conformation. The length of the C8-C9 bond (1.521 Å) was greater than that of the C9-C10 bond (1.4931 Å) and the N(1)-C(9)-C(10)-O(3) and O(2)-C(8)-C(9)-N(1) torsion angles were found to be 175.36 and 92.82(13)°, respectively. These data demonstrate that the double bonds at C8-O2 and C9-N1 did not form a conjugated system, whereas the double bonds at C3-O10 and C9-N1 were conjugated. The carbon-nitrogen double bond in compound **2** existed in the *E* form. Selected bond lengths and bond angles for compound **2** are shown in Table-2.

Intermolecular hydrogen bonds of the type O-H···O and C-H···O were found in the crystal structure of oxime **2** (Table-3). Atoms O1, O2 and O3 acted as hydrogen-bond acceptors towards the hydrogen of the H5-O5 and H7-C7 bonds, which led to the formation of supramolecular structures. Non-classical hydrogen-bonds C7-H7---O1 (3.494, 161.3°, symmetry code -x,1-y,1-z) connected two aromatic rings in the horizontal direction. Furthermore, the side chain oximino ester groups were linked together in chains through bifurcated hydrogen bonds between hydrogen H5-O5···O2 (2.916, 123°, symmetry code-x+1,y+1/2,-z+1/2) and H5-O5···O3 (2.826, 144° and symmetry code x,y+1,z) in the vertical direction. The crystal packing in the crystal structure was therefore stabilized by intermolecular hydrogen bonds, which linked the molecules together to form an infinite network. When viewed along the a-axis, the molecules were interlinked by hydrogen bonds (Fig. 2).

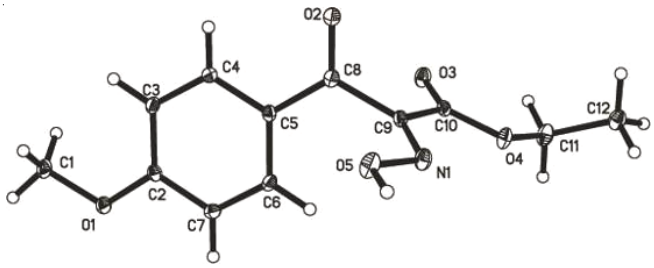


Fig. 1. Molecular structures of oxime **2**, showing the atom-labeling scheme displacement ellipsoids are drawn at the 30 % probability level

TABLE-2
SELECTED BOND LENGTHS (Å)
AND ANGLES (°) FOR COMPOUND **2**

Bond	Dist.	Angle	(°)
O(1)-C(2)	1.3545(12)	C(2)-O(1)-C(1)	117.79(9)
O(3)-C(10)	1.2101(12)	C(9)-N(1)-O(5)	110.20(9)
O(5)-N(1)	1.3892(12)	N(1)-C(9)-C(10)	119.44(10)
C(5)-C(8)	1.4664(14)	C(10)-O(4)-C(11)	118.21(8)
O(1)-C(1)	1.4383(12)	O(2)-C(8)-C(5)	123.45(10)
O(4)-C(10)	1.3243(12)	N(1)-C(9)-C(8)	124.00(9)
O(5)-H(5)	0.8400	N(1)-O(5)-H(5)	109.5
C(8)-C(9)	1.5210(14)	O(2)-C(8)-C(9)	117.75(9)
O(2)-C(8)	1.2209(13)	C(10)-C(9)-C(8)	116.50(9)
O(4)-C(11)	1.4624(13)	–	–
N(1)-C(9)	1.2765(14)	–	–
C(9)-C(10)	1.4931(15)	–	–

TABLE-3
HYDROGEN BONDED GEOMETRIES (°), DISTANCES (Å)
AND BOND ANGLES (°) FOR COMPOUND **2**

D-H···A	d(D-H)	d(H···A)	d(D···A)	∠DHA
O5-H5---O3[a]	0.84	2.10	2.8259(13)	144.0
O5-H5---O2[b]	0.84	2.38	2.9157(14)	123.0
C7-H7---O1[c]	0.95	2.58	3.4936	161.3

Symmetry codes: (a) x,y+1,z; (b) -x+1,y+1/2,-z+1/2; (c) -x,1-y,1-z

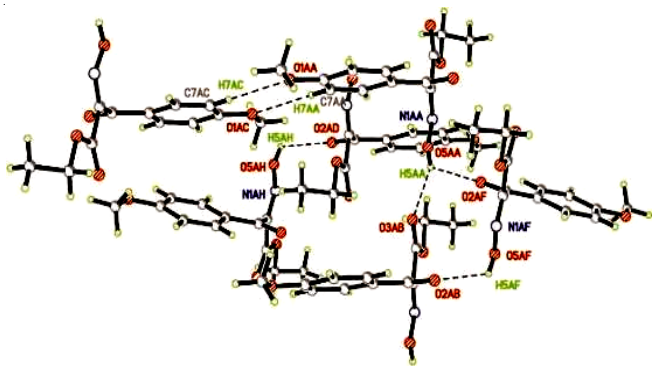


Fig. 2. Hydrogen bonding system between molecules of oxime **2**. The dashed lines represented the intermolecular hydrogen bonds (H-bonds have been drawn between the donor and acceptor atoms)

Crystal structure of compound 3: Selected bond lengths and bond angles for the non-hydrogen atoms in compound **3** are shown in Table-4. The bond lengths and bond angles for compound **3** were found to be in good agreement with the standard. The crystal structure of compound **3** is shown in Fig. 3. The structure was composed of two *erythro-N*-acetyl-β-(4-methoxyphenyl)serine ethyl ester molecules, which existed as enantiomers. One of the molecules (*i.e.*, C1-C14) was in the *S,S*-configuration, whereas the other molecule (*i.e.*, C15-C28) was in the *R,R*-configuration. This X-ray structure therefore confirmed that compound **3** was a racemic mixture. Intermolecular hydrogen bonds of the type O-H···O and N-H···O were found in the crystal structure of compound **3** (Table-5). Atoms O2, O3, O6 and O8 acted as hydrogen-bond acceptors to the hydrogen atoms of the N1-H1, O4-H4, N2-H2 and O9-H9 bonds, respectively, to generate the supramolecular structure (Fig. 4). Four molecules in *S,S*-configuration were linked together by hydrogen bonds between N1-H1---O2 (2.928, 164°) and O4-H4---O3 (2.736, 175°) to form a large ring. Four molecules in the *R,R*-configuration were linked together by hydrogen bonds between N2-H2---O6 (2.969, 165°) and O9-H9---O8 (2.722, 175°) to form another large ring. The two planes of the large rings were perpendicular to each other and the molecules were interlinked through a network of hydrogen bonds (Fig. 4).

Conclusion

An efficient new method has been developed for the facile synthesis of (±)-*erythro*-**3** from oxime **2**. The conformations of (*E*)-oxime 2 and *erythro*-**3** were unambiguously confirmed by X-ray crystallography. We are currently investigating the synthesis of several other oxime ester and *erythro*-amino acid derivatives in our laboratory and this work will be published in due course.

TABLE-4
SELECTED BOND LENGTHS (Å) AND ANGLES (°) FOR COMPOUND **3**

Bond	Dist.	Angle	(°)
C1-C2	1.471 (4)	C3-O1-C2	116.5 (2)
C15-C16	1.481 (4)	C17-O7-C16	116.7 (2)
O1-C2	1.461 (3)	C12-N1-C4	123.0 (2)
O7-C16	1.460 (3)	C27-N2-C18	122.1 (2)
N1-C4	1.444 (3)	N1-C4-C3	112.1 (2)
N1-C12	1.338 (3)	N1-C4-C5	107.98 (18)
O4-C5	1.414 (3)	O3-C12-N1	121.0 (2)
O5-C14	1.398 (6)	N1-C12-C13	116.1 (2)
N2-C18	1.457 (3)	N2-C18-C17	122.1 (2)
N2-C27	1.336 (3)	N2-C18-C19	108.37 (19)
O9-C19	1.413 (3)	O8-C27-N2	121.1 (2)
O10-C23	1.392 (4)	N2-C27-C28	115.7 (2)

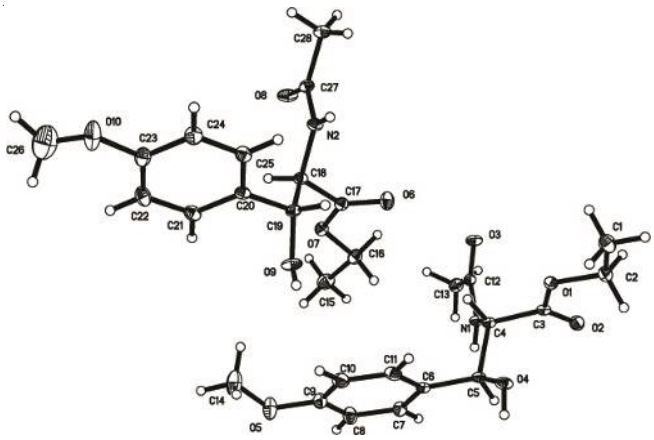


Fig. 3. Molecular structures of compound **3**, showing the atom-labeling scheme. Displacement ellipsoids have been drawn at the 10 % probability level

TABLE-5
HYDROGEN BONDED GEOMETRIES (°), DISTANCES (Å) AND ANGLES (°) FOR COMPOUND **3**

D-H···A	d(D-H)	d(H···A)	d(D···A)	∠DHA
N1-H1---O2[a]	0.86	2.09	2.928(13)	164
N2-H2---O6[b]	0.86	2.13	2.969(3)	165
O4-H4---O3[c]	0.82	1.92	2.736(2)	175
O9-H9---O8[c]	0.82	1.90	2.722(2)	175

Symmetry codes: (a) -x,2-y 1-,z; (b) -x+1,2-y,-z; (c) -1+x,y,z

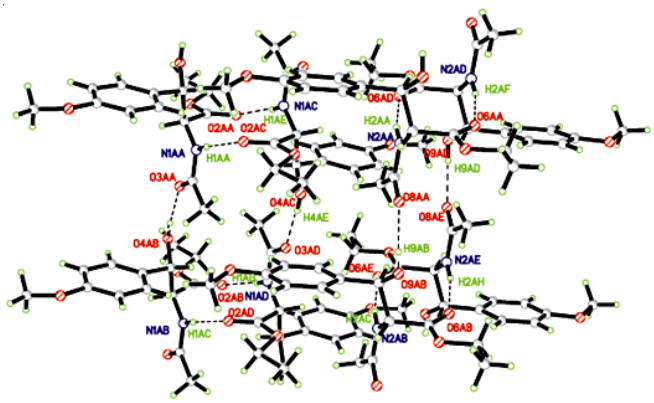


Fig. 4. Hydrogen bonding system between the molecules of **3**. The dashed lines represented the intermolecular hydrogen bonds (H-bonds have been drawn between the donor and acceptor atoms).

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 nos. CCDC-82607 and CCDC-1014816. Copies of the 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).

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