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ORIGINAL PAPER

The Synthesis and Crystal Determination of 3-Hydroxy-4-(4-methoxyphenyl)-5-(2-nitrophenyl)furan-2(5H)-one

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Abstract The title compound, $C_{17}H_{13}NO_6$, was synthesized and structurally characterized by elemental analysis, MS, ^{1}H NMR and single crystal X-ray diffraction. It crystallizes in monoclinic system space group *C 2/c* with $a = 27.981(6)$ Å, $b = 12.996(3)$ Å, $c = 8.0900(16)$ Å, $\beta = 91.06(3)°$, $V = 2941.4(10)$ Å^3, $Z = 8$, $R_1 = 0.0675$, $wR_2 = 0.1626$, and $T = 298(2)$ K. The X-ray structure determination revealed that the center furanone ring is nearly coplanar with *p*-methoxybenzene ring and forms a dihedral angle of 87.2(1)° with the nitrobenzene ring. O–H···O Intermolecular hydrogen bonds link pairs of molecules into centrosymmetric dimers, making a graph set motif of $R_2^2(10)$. The dimers are further assembled into a chain of edge-fused $R_4^4(34)$ rings running along the [001] direction. The final three-dimensional supramolecular architecture is stabilized by weak π–π interactions.

Keywords Synthesis · Crystal structure · 4,5-Diphenylfuran-2(5*H*)-one

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Introduction

Vitamin C, one of the most potent naturally occurring antioxidants, plays an important part in the prevention of a large number of chronic diseases [1]. 3-Hydroxyfuran-2-one is a lipophilic analogue of vitamin C, showing better lipophilicity and chemical stability. We therefore focused our efforts to design and synthesize 3-hydroxyfuran-2-ones for biological activity screen. Cotelle reported that 4-aryl-3-hydroxyfuran-2-one is a good inhibitor of HIV-1 integrase [2]. On the other hand, Bailly and Weber reported that 4,5-diaryl-3-hydroxy-2(5*H*)-furanone show excellent antioxidative and anti-inflammatory activities [3, 4]. In the course of our work on screening hydroxy-2(5*H*)-furanones as antibacterial, we synthesized the title compound and herein reported its crystal structure.

Experimental Section

Reagents and Techniques

2-Hydroxy-3-(4-methoxyphenyl)acrylic acid and 1,5-diazabicyclo[5.4.0]undecene (reagent grade) were purchased from Aldrich (U.S.A) and the other chemicals were purchased from Sinopharm Chemical Reagent Co., Ltd (China). Melting points (uncorrected) were determined on a XT4 MP apparatus (Taike Corp., Beijing, China). EI mass spectra were obtained on a Waters GCT mass spectrometer, and ^{1}H NMR spectra were recorded on a Bruker AV-300 spectrometer at 25 °C with TMS and solvent signals allotted as internal standards. Chemical shifts were reported in ppm (δ). Elemental analyses were performed on a CHN-O-Rapid instrument and were within ±0.4% of the theoretical values.

Synthesis of 3-Hydroxy-4-(4-methoxyphenyl)-5-(2-nitrophenyl)furan-2(5*H*)-one

The pyruvic acid (1.94 g, 10 mmol), 2-hydroxy-3-(4-methoxyphenyl)acrylic acid, was dissolved in dry DMF (50 mL, dried over 4A molecular sieves) at 0 °C. 1,5-diazabicyclo[5.4.0]undecene (DBU, 1.60 mL, 10.7 mmol) and methyl iodide (3.0 mL, 60 mmol) were successively added and the solution was stirred at 0 °C for 3 h and then overnight at room temperature. The solution was poured into a mixture of AcOEt (20 mL) and 1 M HCl (60 mL). The organic layer was separated and the aqueous layer was extracted four times with AcOEt (30 mL). The combined organic layers were washed with H_2O (20 mL) and dried over $MgSO_4$. Evaporation of the volatiles in vacuo afforded the methyl pyruvate, which was used without further purification. ^{1}H NMR (DMSO-d_6): 3.76 (s, 3H); 3.79 (s, 3H); 6.38 (s, 1H); 6.92(d, $J = 8.8$ Hz, 2H); 7.71 (d, $J = 8.8$ Hz, 2H); 8.95 (s, 1H).

0.80 mL of DBU (5.35 mmol) was added under stirring to a cold (0 °C) solution of a mixture of the methyl pyruvate (1.1 g, 5 mmol) and 2-nitrobenzaldehyde (0.76 g, 5 mmol) in dry DMF (24 mL, dried over 4A molecular sieves). The mixture was stirred for 4 h at 0 °C and then poured into a mixture of AcOEt (10 mL) and HCl 1 M (50 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt. The organic layers were combined, washed with water, dried over Na_2SO_4 and evaporated in vacuo. The oily residue was then purified by column chromatography on silica gel. The fraction was partially evaporated and furnished colorless blocks of (I), 3-hydroxy-4-(4-methoxyphenyl)-5-(2-nitrophenyl)furan-2(5*H*)-one, suitable for single crystal structure determination. Yield of 74%, mp 204–206 °C, ^{1}H NMR (DMSO-d_6): 3.75 (s, 3H); 6.91 (s, 1H); 6.95(d, $J = 9.0$ Hz, 2H); 7.36 (dd, $J = 5.8$ Hz, $J = 3.3$ Hz, 1H); 7.53(d, $J = 8.9$ Hz, 2H); 7.67 (dd, $J = 5.7$ Hz, $J = 3.6$ Hz, 1H); 8.06 (dd, $J = 5.8$ Hz, $J = 3.6$ Hz, 1H); 11.00 (s, 1H); EIMS *m/z* 327 (M^+). Anal. Calcd for $C_{17}H_{13}NO_6$: C, 62.39; H, 4.00; N, 4.28; Found: C, 62.44; H, 3.99; N, 4.25.

X-ray Structure Determination of I

X-ray diffraction data were collected using a Bruker SMART APEX CCD diffractometer with graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) at room temperature. A crystal with dimensions 0.2 mm × 0.1 mm × 0.1 mm was used. Data having theta less than or equal to 25° were integrated and the structure was solved by the direct method using the SHELXS-97 program [5], which refined by the full-matrix least-squares method using the SHELXL-97 program [5]. Crystal data and experimental details are listed in Table 1, fractional coordinates and equivalent isotropic thermal parameters in Table 2. H atoms were positioned geometrically and refined as riding atoms, with C–H of 0.93 Å for aromatic H atoms, 0.96 Å for CH_3 groups, 0.98 Å for CH groups and O–H of 0.82 Å, U_{iso}(H) values were set at 1.2 times U_{eq}(C) for aromatic H atoms and CH, 1.5 times U_{eq}(C) for CH_3 and 1.5 times U_{eq}(O) for O–H groups.

Table 1 Crystal data and experimental crystallographic details

Empirical formula	$C_{17}H_{13}NO_6$
Formula weight	327.28
Temperature (K)	298(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	C 2/c
Cell dimensions	
a (Å)	27.981(6)
b (Å)	12.996(3)
c (Å)	8.0900(16)
α (°)	90
β (°)	91.06(3)
γ (°)	90
Volume(Å^3)	2941.4(10)
Z	8
Density (calculated) (Mg/m^3)	1.478
Absorption coefficient (mm^{-1})	0.114
F_{000}	1360
Crystal size	0.2 mm × 0.1 mm × 0.1 mm
θ range for data collection	1.46–25.18°
Index ranges	$-33 \le h \le 33$
	$0 \le k \le 15$
	$0 \le l \le 9$
Reflections collected/Unique reflections	2707/2652
R_{int}	0.0303
Refinement method	Full-matrix least-squares on *F*2
Data/restraints/parameters	2652/1/217
Goodness-of-fit on F^2	1.071
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0675$, $wR_2 = 0.1271$
R indices (all data)	$R_1 = 0.1626$, $wR_2 = 0.1958$
Largest diff. peak and hole (eÅ^{-3})	0.235/−0.236

Results and Discussion

The title compound (I), 3-hydroxy-4-(4-methoxyphenyl)-5-(2-nitrophenyl)furan-2(5*H*)-one, crystallizes in the monoclinic space group *C 2/c* and the structure of (I) with the corresponding atomic numbering scheme is shown in Fig. 1. The bond lengths and angles of the center unsaturated

Table 2 Atomic coordinates and equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U(eq)
C1	0.92366(19)	0.6932(4)	0.1977(7)	0.0913(18)
C2	0.89694(14)	0.5194(3)	0.2370(5)	0.0524(10)
C3	0.86326(15)	0.4555(3)	0.3039(5)	0.0574(11)
C4	0.86743(14)	0.3505(3)	0.2915(5)	0.0574(12)
C5	0.90569(13)	0.3042(3)	0.2115(5)	0.0460(10)
C6	0.94058(14)	0.3717(3)	0.1515(6)	0.0580(12)
C7	0.93575(15)	0.4763(3)	0.1601(5)	0.0633(12)
C8	0.90993(12)	0.1934(3)	0.1991(4)	0.0442(9)
C9	0.87465(13)	0.1195(3)	0.2761(4)	0.0431(9)
C10	0.93250(15)	0.0274(3)	0.1464(6)	0.0630(12)
C11	0.94215(13)	0.1348(3)	0.1232(5)	0.0502(11)
C12	0.82543(13)	0.1251(3)	0.2048(5)	0.0443(10)
C13	0.78078(14)	0.1339(3)	0.2887(5)	0.0438(9)
C14	0.73843(15)	0.1339(3)	0.2144(6)	0.0572(12)
C15	0.73354(16)	0.1264(3)	0.0417(5)	0.0564(11)
C16	0.77578(19)	0.1159(3)	-0.0478(6)	0.0674(13)
C17	0.81915(16)	0.1169(3)	0.0323(5)	0.0541(11)
N1	0.78123(13)	0.1439(3)	0.4734(4)	0.0493(9)
O1	0.88819(11)	0.6216(2)	0.2518(4)	0.0756(10)
O2	0.98134(10)	0.1681(2)	0.0411(4)	0.0718(10)
O3	0.95401(11)	−0.0483(2)	0.1004(4)	0.0784(11)
O4	0.89231(9)	0.0175(2)	0.2363(4)	0.0604(8)
O5	0.74294(11)	0.1265(3)	0.5390(4)	0.0749(10)
O6	0.81632(12)	0.1703(3)	0.5467(4)	0.0761(10)

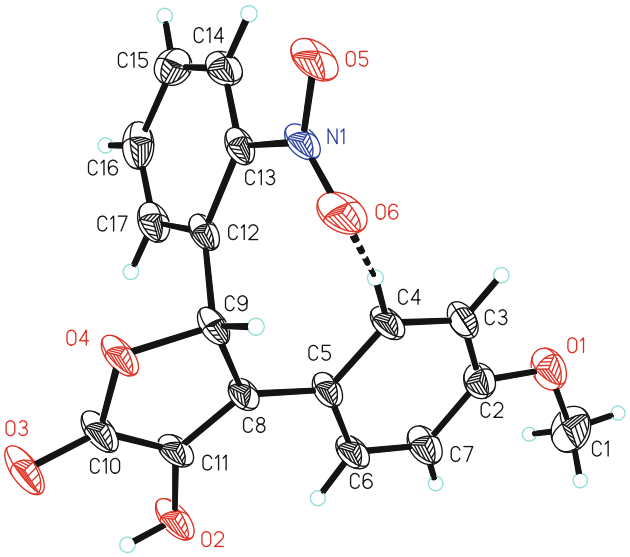

Fig. 1 Molecular structure of compound (I). Displacement ellipsoids are drawn at the 30% probability level. *Dashed lines* indicate hydrogen bonds

lactone ring are within the ranges reported for analogues [6] (Table 2). C8–C11–O2 portion shows clear enol group character with C8–C11 and C11–O2 bond lengths of

Table 3 Selected bond lengths (Å) and bond angles (°) of Compound I

Bond	Dist.
C(5)–C(8)	1.448(5)
C(9)–O(4)	1.454(4)
C(10)–O(3)	1.215(5)
C(11)–C(8)	1.338(5)
C(13)–N(1)	1.500(5)
O(6)–N(1)	1.188(4)
C(8)–C(9)	1.519(5)
C(10)–O(4)	1.357(5)
C(10)–C(11)	1.436(6)
C(11)–O(2)	1.363(4)
O(5)–N(1)	1.225(4)
Angle	**(°)**
C(5)–C(8)–C(9)	123.0(3)
C(9)–C(8)–C(11)	106.1(3)
O(6)–N(1)–C(13)	120.9(3)
O(5)–N(1)–O(6)	124.0(4)
C(5)–C(8)–C(11)	130.8(4)
C(8)–C(9)–C(12)	114.5(3)
O(5)–C(13)–N(1)	115.1(4)

1.338(5) and 1.363(4) Å respectively, which are close to those of typical enol-lactone [7, 8].

The enol-lactone motif and *p*-methoxybenzene ring are nearly coplanar with the mean deviation of 0.0272 Å. In comparison with C5–C8–C9 angle (123.1(3)°) (Table 3), the mildly increased C5–C8–C11 angle (130.9(3)°) may result from the coplanar atoms (H16 and O2) increasing their steric strain. This was supported by the other reported analogues [6, 7, 9]. In those compounds, the bigger the dihedral angle between enol-lactone motif and the attached benzene ring is, the smaller the above mentioned angle is. The nitro group is tilted out of the mean plane that it attached by 18.0(2)°, which is significantly higher than that observed in the other nitrobenzenes [10, 11]. The increase in the dihedral angle may be attributed to the presence of the C4–H4···O6 hydrogen bond represented by a graph-set motif of S(9), which increases the torsion angle of C12–C13–N1–O6 (19.1(5)°) (Fig. 1). The tiltation of nitro group is therefore disrupted the conjugation with its attached benzene ring, and elongate the bond length of C13–N1 from about 1.46 Å [10, 11] to 1.500(5) Å. The pendent aryl ring (C12–C17) is almost vertical to the enol-lactone ring with the dihedral angle of 87.2(1)°.

In (I), there is a single O–H···O hydrogen bond utilizing the enolic hydroxyl group as the donor (Table 4), and this links pairs of molecules into centrosymmetric dimers characterized by a graph-set motif of $R_2^2(10)$ (Fig. 2). In the

Table 4 Hydrogen-bond geometry (Å, °)

D–H···A	D–H	H···A	D···A	D–H···A
O2–H2A···O3	0.82	2.59	2.956(4)	109
C4–H4···O6	0.93	2.60	3.450(5)	152
C6–H6···O2	0.93	2.38	3.022(5)	126
C9–H9···O6	0.98	2.11	2.832(5)	129
C14–H14···O5	0.93	2.28	2.628(6)	101
O2–H2A···O3^{i}	0.82	1.89	2.662(4)	157
C16–H16···O5^{ii}	0.93	2.57	3.453(6)	159

Symmetry transformations used to generate equivalent atoms: i = $-x + 2, -y, -z$; ii = $x, y, z - 1$

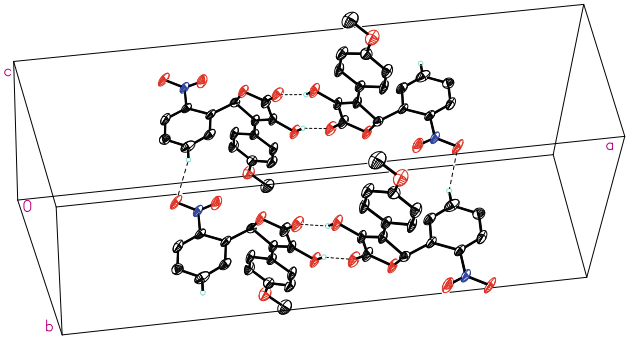

Fig. 2 Part of the crystal structure of (I), showing the formation of a hydrogen bonded dimer and R_4^4 motif built from paired O–H···O and C–H···O hydrogen bonds (*dashed lines*). For the sake of clarity, the H atoms not involved in the hydrogen bonds have been omitted

dimers packing along c-axis, the *p*-methoxyphenylenol-lactone motifs of the molecules at (x, y, z) and (−x + 2, −y, −z) are in lines (the least square line through all atoms of the *p*-methoxyphenylenol-lactone motif) alternatively running along the [233] and $[\bar{2}33]$ directions, which lie parallel to the $(01\bar{1})$ plane. However, the pendent *o*-nitrophenyl rings are strictly parallel, with an interplanar spacing of 2.502(4) Å. A relatively weak C16–H16···O5 interactions connect the dimers via interaction of one nitrophenyl ring with another, forming a $R_4^4(34)$ ring (Fig. 2). The combination of these motifs generates a chain of edge-fused rings running along the [001] direction, with $R_4^4(34)$ rings centered at (0, 0, n/2), where n represents an integer. The dimers along the other direction, alternatively presented in this chain, generate another chain (Fig. 3). A co-chain is therefore formed with an "x" pattern of the cross section.

In the structure of (I), weak π–π interactions were found between nitrobenzene rings at (x, y, z) and those at (−x + 1/2, −y + 1/2, −z + 1), with minimum centroid separations of 4.111(3) Å (Fig. 4). These weak intermolecular contacts consequently link the above mentioned co-chains into a three dimensional network.

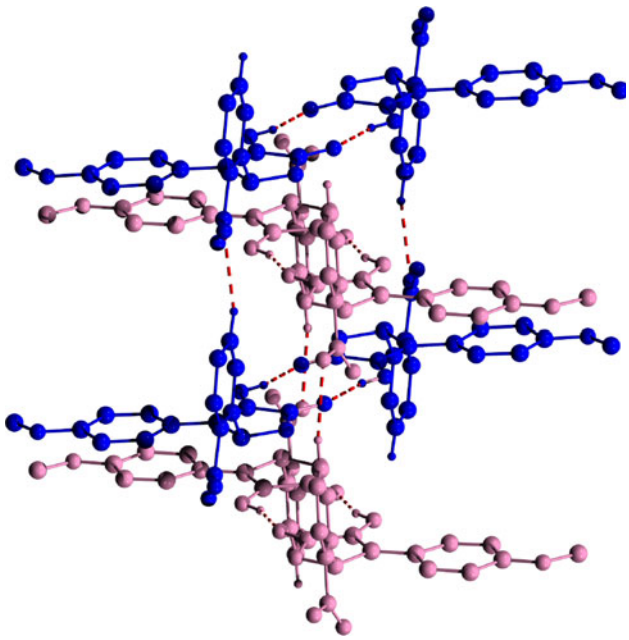

Fig. 3 Part of the crystal structure of (I), showing the formation of the co-chain. *Solid dashed line* indicate hydrogen bonds. For the sake of clarity, the H atoms not involved in the hydrogen bonds have been omitted

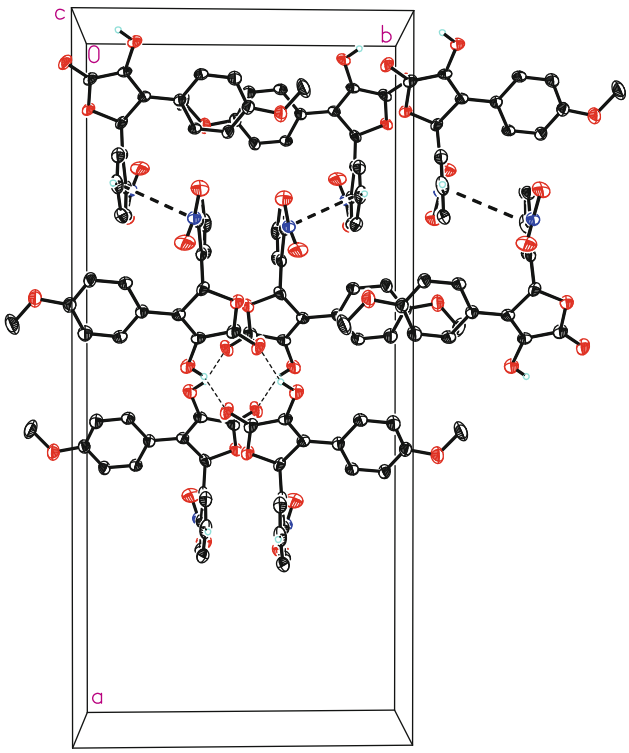

Fig. 4 Packing diagram of compound (I) viewing along c-axis, *Solid dashed lines* indicate π–π interactions

Supplementary Material

CCDC deposit number of CCDC 787202 for I contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre(CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223-336033; e-mail:deposit@ccdc.cam.ac.uk].

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