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Crystal structure of 5,5-dimethyl-3-oxocyclohex-1-en-1-yl 4-(2,2-dichloroacetyl)-3,4-dihydro-2 *H*-benzo[*b*][1,4]oxazine-7-carboxylate, C₁₉H₁₉Cl₂NO₅

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Abstract

C₁₉H₁₉Cl₂NO₅, orthorhombic, *Pbca* (no. 61), *a* = 12.6750(18) Å, *b* = 11.0927(17) Å, *c* = 28.400(4) Å, *V* = 3993.0(10) Å³, *Z* = 8, *R*_{gt}(*F*) = 0.0700, *wR*_{ref}(*F*²) = 0.2011, *T* = 293(2) K.

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The crystal structure is shown in the figure (Hydrogen atoms are omitted for clarity). Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

Methyl 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylate was synthesized with methyl 4-amino-3-hydroxybenzoate (18 mmol) and 1,2-dibromoethane (22 mmol) as raw materials, anhydrous K₂CO₃ (90 mmol) as the attaching acid agent in 50 mL DMAC, refluxed for 7 h at 80 °C (monitored by TLC) [4]. After the reaction, K₂CO₃ was removed by vacuum

Table 1: Data collection and handling.

Crystal:	Block, colorless
Size:	0.15 × 0.12 × 0.10 mm
Wavelength:	Mo Kα radiation (0.71073 Å)
μ:	0.35 mm ^{−1}
Diffraction, scan mode:	Bruker D8 VENTURE PHOTON II, φ and ω-scans
θ _{max} , completeness:	28.4°, >99%
<i>N</i> (<i>hkl</i>) _{measured} , <i>N</i> (<i>hkl</i>) _{unique} , <i>R</i> _{int} :	35421, 4974, 0.067
Criterion for <i>I</i> _{obs} , <i>N</i> (<i>hkl</i>) _{gt} :	<i>I</i> _{obs} > 2 σ(<i>I</i> _{obs}), 2812
<i>N</i> (<i>param</i>) _{refined} :	246
Programs:	Bruker programs [1], SHELX [2], DIAMOND [3]

filtration, and the organic phase was separated with saturated salt water and ethyl acetate. The solution was dried by anhydrous Na₂SO₄ for 30 min, and then Na₂SO₄ was removed by vacuum filtration. The solvent was removed under vacuum. The crude product, red-brown solid was purified on silica gel by column chromatography [V(ethyl acetate):V(petroleum ether)=1:3] until a brown solid, methyl 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylate, was obtained in 30% yield [5]. Methyl 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylate (2.02 mmol) and 5% NaOH aq. (15 mL) were added to 25 mL EtOH to reflux for 5 h at 65 °C. After the reaction, the solution was diluted with water, cooled to room temperature, adjusted to pH = 5–6 with concentrated hydrochloric acid, extracted with CHCl₃, and the organic layer was dried over anhydrous Na₂SO₄ for 30 min. Na₂SO₄

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
Cl1	0.80420(11)	1.21969(12)	0.06655(5)	0.1024(5)
Cl2	0.62195(10)	1.07126(13)	0.04608(4)	0.0920(4)
N1	0.67630(19)	0.9859(3)	0.15407(9)	0.0524(7)
O1	0.8318(2)	0.9969(3)	0.11574(11)	0.0948(11)
O2	0.52355(16)	0.8104(2)	0.17957(9)	0.0680(7)
O3	0.6905(2)	0.5503(3)	0.30061(10)	0.0808(9)
O4	0.86288(17)	0.5906(2)	0.29452(8)	0.0621(7)
O5	0.9617(4)	0.2522(3)	0.38214(15)	0.1489(19)
C1	0.7004(3)	1.1364(4)	0.09129(13)	0.0689(10)
H1	0.6566	1.1895	0.1108	0.083 [*]
C2	0.7438(3)	1.0328(3)	0.12162(12)	0.0622(9)
C3	0.5632(3)	1.0163(3)	0.15892(13)	0.0626(9)
H3A	0.5450	1.0812	0.1375	0.075 [*]
H3B	0.5486	1.0429	0.1908	0.075 [*]
C4	0.4995(3)	0.9079(3)	0.14788(13)	0.0632(9)
H4A	0.4252	0.9276	0.1502	0.076 [*]
H4B	0.5137	0.8827	0.1158	0.076 [*]
C5	0.6247(2)	0.8044(3)	0.19542(11)	0.0488(7)
C6	0.7045(2)	0.8858(3)	0.18279(10)	0.0466(7)
C7	0.8047(2)	0.8701(3)	0.20146(12)	0.0552(8)
H7	0.8586	0.9226	0.1928	0.066 [*]
C8	0.8253(2)	0.7782(3)	0.23246(11)	0.0529(8)
H8	0.8929	0.7688	0.2447	0.063 [*]
C9	0.7457(2)	0.6995(3)	0.24560(10)	0.0482(7)
C10	0.6457(2)	0.7122(3)	0.22676(11)	0.0526(8)
H10	0.5925	0.6587	0.2352	0.063 [*]
C11	0.7598(3)	0.6060(3)	0.28245(11)	0.0550(8)
C12	0.8802(2)	0.5307(3)	0.33723(11)	0.0509(8)
C13	0.9125(3)	0.4178(4)	0.33704(13)	0.0691(10)
H13	0.9198	0.3769	0.3087	0.083 [*]
C14	0.9366(4)	0.3570(4)	0.38123(16)	0.0835(13)
C15	0.9331(3)	0.4297(4)	0.42524(13)	0.0702(10)
H15A	1.0018	0.4659	0.4303	0.084 [*]
H15B	0.9190	0.3764	0.4516	0.084 [*]
C16	0.8505(3)	0.5285(3)	0.42455(12)	0.0580(8)
C17	0.8672(3)	0.6037(3)	0.38008(12)	0.0650(9)
H17A	0.8072	0.6570	0.3760	0.078 [*]
H17B	0.9294	0.6535	0.3842	0.078 [*]
C18	0.8626(5)	0.6085(5)	0.46788(16)	0.1056(17)
H18A	0.9321	0.6428	0.4683	0.158 [*]
H18B	0.8521	0.5611	0.4958	0.158 [*]
H18C	0.8111	0.6719	0.4668	0.158 [*]
C19	0.7407(3)	0.4741(5)	0.42446(15)	0.0827(13)
H19A	0.6892	0.5374	0.4228	0.124 [*]
H19B	0.7303	0.4286	0.4528	0.124 [*]
H19C	0.7331	0.4219	0.3977	0.124 [*]

was removed by vacuum filtration, and then the solvent was removed under vacuum evaporating to obtain a light brown powder, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carboxylic acid in 90% yield [6]. The acid (6.7 mmol) was dissolved in 25 mL THF, and 2,2-dichloroacetyl chloride (8.0 mmol) was added, whereas the reaction mixture was

cooled by an ice-water bath. The mixture was reacted at room temperature for 2 h. After the reaction, the solvent was removed under vacuum. The crude product was washed with 30 mL CH₂Cl₂, and then the solvent was removed by filtration. Repeating three times to remove unreacted acid chloride. Light brown solid, 4-(2,2-dichloroacetyl)-3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxylic acid was obtained in 96% yield. The acid (16.2 mmol) and SOCl₂ (48.6 mmol) were dissolved in 25 mL THF, and DMF (5 drops) were used as catalyst. The mixture was refluxed for 2 h at 65 °C. After the reaction, the solvent was removed under vacuum evaporating to obtain 4-(2,2-dichloroacetyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-carbonyl chloride. The acid chloride (10.6 mmol) was reacted with 5,5-dimethylcyclohexane-1,3-dione (12.7 mmol), Et₃N (31.8 mmol) as the attaching acid agent in 25 mL THF (monitored by TLC). After the reaction an orange solid of the title compound was obtained in 81% yield.

Experimental details

The C—H atoms were then constrained to an ideal geometry, with C—H distances of 0.93–0.96 Å. The *U*_{iso} values of the hydrogen atoms of methyl groups were set to 1.5*U*_{eq}(C_{methyl}) and the *U*_{iso} values of all other hydrogen atoms were set to 1.2*U*_{eq}(C).

Discussion

Cyclohexanedione derivatives were critically important used as synthons and biological activities materials [7]. They were also used as medical or pharmaceutical intermediates [8], which have received great interest because of their excellent pharmacological activity and biological activity, organic synthesis intermediates, and agricultural chemicals [9–11]. 4-Hydroxyphenylpyruvate dioxygenase (HPPD), a target for green herbicide discovery, has attracted a large number of attention owing to controlling efficacy of resistant weeds [12, 13]. It is an important enzyme in the tyrosine metabolic pathway, belonging to the large family of 2-his-1-carboxylate facial triad oxidative enzymes. As an important enzyme correlated to the pigment synthesis and tyrosine catabolism in most organisms, HPPD is important in agricultural areas [14]. A large number of HPPD inhibitors have been discovered, researched and applied to control weed in the field of agrochemicals in recent several decades [15]. Based on our previous efforts to find novel HPPD-inhibiting compounds [16], herein we reported the synthesis and the crystal structure of substituted benzoxazine-cyclohexanedione.

In the crystal structure, the distance of C12–C13 (1.318(5) Å) is closer to the typical C=C bond, and the C13–C14 bond (1.457(6) Å) is shorter than typical C–C bond which is made by conjugation of carbonyl and C=C bond (C12–C13). The N atom and O atom form a conjugated system with

benzene ring while methylene group does not. The carbonyl (C2=O1) forms a conjugated system with the oxazine ring. The mean plane of the cyclohexanedione is almost perpendicular to the mean plane of the benzoxazine moiety (see the figure). The van der Waals forces connect molecules into a one-dimensional chain structure.

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