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Crystal structure of 1-(4-chloro-2-hydroxy-5-iodophenyl)ethan-1-one, C₈H₆ClIO₂

Table 1: Data collection and handling.

Crystal:	Colourless rod
Size:	0.46 × 0.07 × 0.07 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	3.82 mm ⁻¹
Diffractometer, scan mode:	Bruker D8 Venture Photon, ω
$\theta_{\max}$, completeness:	28.0°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	65860, 2158, 0.034
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 1983
$N(\text{param})_{\text{refined}}$:	114
Programs:	Bruker [1], ORTEP-3 [2], SHELX [3], PLATON [4]

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

Atom	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
C1	0.84530(17)	0.7014(3)	0.45147(12)	0.0189(4)
C2	0.85496(17)	0.7681(3)	0.38144(12)	0.0195(4)
H2	0.91971	0.789074	0.361603	0.023*
C3	0.77010(17)	0.8037(3)	0.34086(11)	0.0176(4)
C4	0.67405(16)	0.7787(3)	0.36951(11)	0.0173(4)
C5	0.66486(17)	0.7165(3)	0.43956(11)	0.0182(4)
H5	0.599781	0.701392	0.459642	0.022*
C6	0.74932(18)	0.6752(3)	0.48176(11)	0.0177(4)
C7	0.73909(18)	0.6015(3)	0.55591(12)	0.0223(5)
C8	0.6372(2)	0.5819(4)	0.58930(13)	0.0292(5)
H8A	0.643305	0.518815	0.635786	0.044*
H8B	0.593875	0.509677	0.55729	0.044*
H8C	0.60782	0.704337	0.596653	0.044*
O1	0.93070(13)	0.6652(3)	0.48769(10)	0.0275(4)
O2	0.81425(14)	0.5555(3)	0.58975(9)	0.0295(4)
Cl1	0.78693(4)	0.87837(8)	0.25322(3)	0.02311(12)
I1	0.54310(2)	0.82672(2)	0.31056(2)	0.02499(6)
H1	0.912(3)	0.626(5)	0.528(2)	0.056(11)*

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Abstract

C₈H₆ClIO₂, orthorhombic, *Pbcn* (no. 60), $a = 13.3204(7)$ Å, $b = 7.2517(4)$ Å, $c = 18.5627(9)$ Å, $V = 1793.07(16)$ Å³, $Z = 8$, $R_{\text{gt}}(F) = 0.0195$, $wR_{\text{ref}}(F2) = 0.0483$, $T = 173$ K.

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The molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

The preparation and analytical data for the title compound have been described before [5]. A stirred mixture of a 4-chloro-2-hydroxyacetophenone (5.00 g, 29.3 mmol) and *p*-toluenesulfonic acid (12.04 g, 35.1 mmol) in acetonitrile (200 mL) at 0 °C was treated with *N*-iodosuccinimide (5.17 g,

29.3 mmol) over 5 min. The mixture was allowed to stir at room temperature for 14 h, and then quenched with an ice-cold saturated aqueous solution of sodium thiosulphate. The precipitate was filtered and recrystallized to afford the title compound as a solid (7.39 g, 85%), mp. 143–145 °C. Single crystals were obtained by slow evaporation of a ethanol solution of the title compound at room temperature.

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Experimental details

Intensity data was determined on a Bruker Venture D8 Photon CMOS diffractometer with graphite-monochromated MoK α_1 (λ 0.71073 Å) radiation at 173 K using an Oxford Cryostream 600 cooler. Data reduction was carried out using the program SAINT+, version 6.02 [1] and empirical absorption corrections were made using SADABS [1]. The structure was solved in the WinGX [2] Suite of programs, using intrinsic phasing through SHELXT [3] and refined using full-matrix least-squares/difference Fourier techniques using SHELXL [3]. All C bound H hydrogen atoms were placed at idealized positions and refined as riding atoms with isotropic parameters 1.2 times those of their parent atoms. The O-bound hydrogen atom were located in the difference fourier map and their coordinates and an isotropic thermal parameter allowed to refine freely. Diagrams and publication material were generated using ORTEP-3 [2], and PLATON [4].

Comment

Phenyl methyl ketones (acetophenones) are a class of aromatic compounds produced by plants in response to stress or as protection reaction against parasites or herbivores [6]. Halogenated 2-hydroxyacetophenones are important intermediates in the synthesis of polysubstituted and polycyclic flavonoid derivatives. The reactions of 2-hydroxyacetophenones with the Vilsmeier-Haack reagent, for example, afford chromone-3-carbaldehyde derivatives with potential anti-inflammatory activity [7] and inhibitory effect against protein tyrosine phosphatase 1B [8], thymidine phosphorylase [9], carbonic anhydrase [10], and metallo- β -lactamase [11]. Claisen-Schmidt aldol condensation of the 2-hydroxyacetophenones with substituted benzaldehydes, on the other hand, furnishes chalcone derivatives with a wide range of biological properties [12]. The presence of the *ortho*-hydroxy-*trans*- α,β -unsaturated carbonyl moiety facilitates acid or base mediated cycloisomerization into the corresponding flavanones or oxidative cyclization to afford flavones, isoflavones and flavonol derivatives [13]. We have previously reported the synthesis and *in vitro* inhibitory effect of a series of 4-halogeno-2-hydroxy-5-iodochalcones and their 7-halogeno substituted 2-aryl-3-hydroxy-6-iodo-4*H*-chromen-4-one derivatives against acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and β -secretase (BACE1) activities [5]. The 4-halogeno-2-hydroxy-5-iodochalcones were, in turn, prepared *via* a Claisen-Schmidt aldol condensation of the 4-halogeno substituted 2-hydroxy-4-iodoacetophenones with benzaldehyde derivatives. Aryl and heteroaryl iodides in radioiodinated form are routinely used in single photon emission computed tomography (SPECT) imaging for the clinical diagnosis of disease and drug development [14].

Moreover, the reactivity of the carbon-iodine bond allows facile oxidative addition and subsequent application as organometallic reagents in cross-coupling reactions.

Small model systems with intramolecular and/or intermolecular hydrogen bonds such as the 2-hydroxyacetophenones are often employed to study these interactions in the solid state [15]. Hydrogen bond formation causes changes in the distances between atoms and the rearrangement of electron densities on the groups involved in the interaction and therefore chemical reactivity especially if the reaction centres are directly involved in the hydrogen bonding [16]. Likewise, halogen bonding and halogen-halogen interactions continue to attract considerable attention in medicinal chemistry, chemical biology, supramolecular chemistry and crystal engineering [17–20]. Our continued interest in hydrogen and halogen bonding [21, 22] prompted us to study the structure of the 4-substituted 2-hydroxy-5-iodoacetophenones in the solid state by single crystal X-ray diffraction (XRD) method.

Single crystals of 1-(4-chloro-2-hydroxy-5-iodophenyl) ethanone (4-chloro-2-hydroxy-5-iodoacetophenone) suitable for X-ray diffraction analysis were obtained by slow evaporation of ethanol. The crystallographic numbering in the above figure has been used in the context of the X-ray analysis and differs with the systematic numbering for these compounds. Single crystal XRD analysis confirmed the existence of one molecule in the asymmetric unit (*cf.* the figure) with intramolecular hydrogen bond involving the hydroxyl group (donor) and the oxygen atom (acceptor) of the carbonyl group with hydrogen bond distance, $d(O(1)-H(1)\cdots O(2)=1.81$ Å. Due to involvement in hydrogen bonding, the carbonyl C=O bond is longer 1.228 Å as compared to a typical acetophenone (1.216 Å) [23]. The molecules exist in the crystal lattice as stacked in anti-parallel chains, each chain held together by a combination of aromatic-aromatic stacking interactions, and intra- and intermolecular O–H $\cdots$ O hydrogen bonding interactions. Apart from the differences in C–I and C–Cl bond lengths 2.088 Å and 1.729 Å, respectively, PLATON analysis [24] revealed the involvement of chlorine atom as an electron density acceptor in contact with the carbonyl oxygen (3.09 Å). Such halogen bond interaction is not observed with iodine atom though it has the largest σ -hole among the halogen atoms [17, 20]. The I $\cdots$ Cl contacts of about 3.63 Å are essentially close packing van der Waals interactions that connect the two parallel layers together in eight-membered rings. The molecules are involved in aromatic-aromatic stacking interactions, which are known to maintain a favourable geometry between aromatic units [25]. Aromatic-aromatic stacking interactions and halogen contacts are responsible for the supramolecular arrangements of the title structure. These observations should be valuable for rational drug design and

helpful in understanding interactions of halogenated ligands with proteins.

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