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Green synthesis of tetraketones: crystal structure, DFT studies and Hirshfeld surface analysis of 2,2'-((3,4-dimethoxyphenyl) methylene) bis(3-hydroxy-5,5-dimethylcyclohex2-enone)

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ABSTRACT

The present work deals with a practically efficient protocol designed for the synthesis of tetraketones using ultrasound in the presence of boric acid as the catalyst. One of the tetraketone, (**3a**) was confirmed by crystallographic studies. The molecules in crystal lattice are held together by weak intermolecular C–H···O, C–H··· π and intramolecular O–H···O interactions. Hirshfeld surface analysis was carried out for the graphical visualization, while, the 2D fingerprint plots provide percentage contribution of each individual atom-to-atom interactions. Finally, to determine molecular electrical transport properties, we studied the energy difference between highest occupied, HOMO, and lowest unoccupied, LUMO orbitals.

KEYWORDS

Boric acid; crystal structure; tetraketones; theoretical studies; ultrasound

1. Introduction

In recent years, development of environmentally friendly, benign, cost effective and clean synthetic procedures has become the most desired goal in the field of organic synthesis. Organic reactions carried out by green method such as ultrasound employing green solvents are more convenient and environmental friendly compared to traditional methods. Therefore it has attracted much attention, especially from the viewpoints of green chemistry [1]. Green chemistry approaches can lower energy costs, reduce chemical wastage and lesser byproduct formation. The possibility of carrying out organic reactions under green solvents can improve their ecological value [2]. Reactions carried out in aqueous media are environmentally safe, devoid of carcinogenic effects, have simple work up, and are also especially suited for industry [3]. Thus, there is a need for the development of organic reactions in aqueous medium.

Tetraketones are important precursors extensively used in the synthesis of acridinediones and for the synthesis of various heterocyclic compounds [4]. Tetraketones show significant lipoxygenase inhibitor activity and strong anti-oxidant potential [5]. They exhibit broad spectrum of therapeutic and biological properties [6–8]. Synthesis and

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biological application of tetraketone derivatives have received great interest due to their structural similarity to those of biologically important compounds, such as NADH and NADPH [9] and similar properties to those of 1,4-dihydropyridines.

Ultrasonic technique reduces the reaction duration, improves the yield and involves easier work-up procedures than conventional methods [10]. Ultrasound works by the phenomenon of cavitation. Collapse of these cavities creates drastic conditions inside the medium for an extremely short time and temperatures of 2000–5000 K [10,11]. These cavitation-induced effects can cause physical, chemical, and biological transformations more effectively.

The Clasien condensation and Michael addition of aldehydes with active methylene compounds in the presence of acidic or alkaline catalysts are widely used as important versatile precursors for the synthesis of tetraketones [12]. Because of their great practical importance, several methods have been proposed, employing different catalysts and promoters, some of them are NaOH [13], KOH [14], piperidine [15], proline [16], and cetyltrimethyl ammonium bromide (CTMAB) [17]. Furthermore, catalyst-free reactions in pure water [18], in solid state, and in melts have also been reported [19].

Unfortunately, most of the reported protocols are, although efficient, suffer from serious drawbacks, such as high reaction temperature, longer reaction time, low yields, excess use of reagents as well as toxic or expensive catalysts. As a result, we have developed a methodology to syntheses tetraketones which is efficient, green and easily adaptable.

Boric acid in recent years, has acquired a special attention for its catalytic activity in organic syntheses due to its advantages such as excellent solubility in water, uncomplicated handling, inexpensiveness and eco-friendly nature. Therefore, this spurred our interest to investigate the application of boric acid as a catalyst.

Owing to its numerous significance in methodology and the structure, we herein report an ultrasound promoted simple, neat and efficient method for the syntheses of tetraketone derivatives.

2. Experimental

2.1. Materials and methods

Ultrasonication was performed using SIDILU, Indian make sonic bath working at a constant frequency of 35 kHz and an output power of 70 W at 28 °C (maintained by circulating water). The fine chemicals and solvents were purchased from Sigma-Aldrich, Merck and Spectrochem, Bangalore. Melting points were determined in open capillaries using Guna melting point apparatus and are uncorrected. The reactions and purity of the products were monitored by Merck F-254 pre-coated TLC silica gel plates. ¹H NMR and ¹³C NMR were obtained on a Bruker AMX 400 spectrometer using CDCl₃ with tetramethylsilane as internal standard. IR spectra were recorded on Shimadzu FT-IR 8400S and the values are reported in wave number (cm⁻¹).

2.2. General synthetic procedure for syntheses of tetraketones

A mixture of aldehyde (1 mmol), dimedone (2 mmol), and catalytic amount of boric acid was treated with a 1:1 mixture of ethanol-water and placed in a sonic bath and sonicated at $27 \,^{\circ}$ C until the reaction was completed to yield tetraketones (**3a-j**) as



Scheme 1. Syntheses of tetraketones using boric acid in ultrasound condition.

shown in Scheme 1. All the reactions were monitored by thin-layer chromatography (TLC) and after completion of the reaction, the mixture was cooled to room temperature and filtered. The precipitate obtained was washed with water.

2.3. Physical measurement

2-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(3,4-dimethoxyphenyl)methyl)-5,5-dimethylcyclohexane-1,3-dione (**3a**): $C_{25}H_{32}O_6$, molecular weight: 428.51, yield: 80%, m.p. 200 °C, IR (KBr v cm⁻¹): 3298(OH), 1702(C=O), 1596(C=C). ¹H NMR (400 MHz, CDCl₃) δ 1.01 (6H, CH₃, s), 1.12 (6H, CH₃, s), 2.32–2.50 (8H, CH₂, m), 3.79 (6H, OCH₃, s), 5.51 (1H, CH, s), 7.19 (1H, *J* 8.5, Ph-H, d), 11.94 (2H, OH, s).

2-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(4-methoxyphenyl)methyl)-5,5dimethylcyclohexane-1,3-dione (**3c**): C₂₄H₃₀O₅ molecular weight: 398.20, yield: 88%, m.p. 197–200 °C, IR (KBr v cm⁻¹): 3350.33(OH), 1601.26(C = O), 1533.26(C = C). ¹H NMR (400 MHz, CDCl₃) δ 1.12 (6H, CH₃, s), 1.25 (6H, CH₃, s), 2.51–2.29 (8H, CH₂, m), 3.75 (3H, OCH₃, S), 5.53 (1H, CH, s), 6.75–6.66 (m, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 11.57 (1H, OH, s), 11.96 (1H, OH, s), ppm; ¹³C NMR (75 MHz, CDCl₃) d 190.3, 189.3, 159.5, 139.8, 129.0, 119.2, 115.6, 112.9, 111.1, 55.0, 47.1, 46.4, 32.8, 31.4, 29.6, 27.3.

3. Investigation techniques

3.1. X-ray single crystal structure analysis

Crystal of compound **3a** was mounted on a Bruker Smart CCD Area Detector System and the intensity data was collected using MoK α (0.7103 Å) radiation in ω - φ scan mode. The data were reduced using SAINT-Plus [20]. The structure was solved by direct methods and refined on F^2 using SHELX-97 [21] software package. All the nonhydrogen atoms were refined anisotropically. As the hydrogen atoms were not readily revealed from difference Fourier maps, they were included in the ideal positions with fixed isotropic U values, and they were riding with their respective non-hydrogen atoms. The mean plane calculations were done using the program PARST [22]. Diagrams were generated using ORTEP-3 [23] and DIAMOND [24].

3.2. Computational details

Compound **3a** is theoretically explored in detail for the comparative investigation with experimentally obtained results of X-ray diffraction. All calculations were performed by

Entry	Solvent	Time (min)	Yield (%)
1.	CH ₃ CN	120	76
2.	CHCl₃	110	76
3.	CH ₂ Cl ₂	90	85
4.	Water	85	70
5.	C₂H₅OH	75	80
6.	$C_2H_5OH^-H_2O$	80	95

Table 1. Optimization of solvent for the syntheses of tetraketones derivatives in ultrasound conditions.

Gaussian 16 software package [25] and were visualized using Gauss View six without any constraints on the geometry [26]. Density Functional Theory (DFT) calculations using B3LYP method proposed by Becke [27,28]. Geometry optimizations were performed using 6-311+G (d,p) basis set [29,30]. The structure was optimized without any constraints. DFT optimized structure was confirmed to be minima on potential energy surface (PES) by performing harmonic vibration frequency analysis (no imaginary frequency found). No symmetry constraints were applied and only the default convergence criteria were used during the geometric optimizations. The frontier molecular orbital energies were calculated using 6-311+G (d,p) basis set. In addition to this, molecular electrostatic potential map (MEP) was obtained from the output of B3LYP/6-311+G (d,p) basis set.

4. Results and discussion

In continuation of our studies to synthesize pharmaceutically important tetraketones, green procedures were employed. Herein, we wish to report the synthesis of tetraketones in the presence of boric acid under ultrasound irradiation Scheme 1. Initially, a sample reaction was carried out using benzaldehyde (1 mmol), dimedone (2 mmol), and boric acid as a suitable catalyst in the presence of ethanol-water mixture as solvent for the synthesis of **3b**. The results are summarized in Table 2. It can easily be seen that the condensation of a series of aldehydes with dimedone leads to the formation of tetraketones (**3a-j**) in good yields under ultrasound irradiation (35 kHz) in the presence of a Bronsted acid such as boric acid and a mixture of ethanol-water as solvent when compared to other solvent systems as seen in the Table 1. As shown in Table 2, various aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents can be obtained in high yields. It is more appealing to know the remarkable stability of a variety of functional groups such as hydroxyl, nitro, and other substituents.

The methodology involves ultrasound in aqueous – ethanol medium. All the products were formed in less than an hour. The formation of tetraketones (3a-j) from dimedone and aromatic aldehyde in the presence of boric acid can be explained by a plausible mechanism presented in Fig. 1. Initially activation of substituted benzaldehyde (1) takes place with boric acid followed by attack of enol form of dimedone (2) to give an intermediate (3) by loss of water molecule through Clasien-condensation mechanism. Finally the second molecule of dimedone undergoes Micheal addition with intermediate three furnishing the products 3a-j.

Compound no.	R/substituent	Yield (%)	Time (min)	Melting point (°C) (literature value) [Ref. no.]
3a	<u>\</u> 0	80	45	200–202
3b		82	30	202–204 (194–195) [35]
3c		88	42	198–200 (197–200) [35]
3d		79	34	192–194 (197–198) [35]
3e	OH O HO	90	40	185–187 (187–189) [35]

 Table 2. Isolated yields and time duration for formation of tetraketones 3a-3j.

(continued)

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Table 2. Continued.

Compound no	P/substituent	Viold (%)	Time (min)	Melting point (°C)
3f		89	40	171–173 (175–177) [35]
	OH O			
3g	OH O HO	89	35	190–192 (188–190) [35]
3h	OH O HO HO	86	43	195–197 (195–196) [36]
3i	ОН ОН	90	45	201–203 (205–206) [36]
3j	OH OF HO	84	40	187–189 (194–195) [29]



Figure 1. Plausible mechanism for the formation of tetraketones with boric acid 3a-j.

4.1. Crystallographic studies

Appropriate crystals of compound **3a** were obtained from slow evaporation method using ethylacetate as solvent at room temperature and subjected to single crystal X-ray diffraction analysis. A good quality single crystal was mounted along its largest dimension and used for data collection. Crystallographic data and other structure refinement parameters of the compound **3a** are given in Table 3. Weak interaction parameters in compound **3a** is given in Table 4. The ORTEP view of the molecules **3a** with atomic labeling (thermal ellipsoids drawn at 50% probability) is shown in Fig. 2. Figure 3 of compound **3a** shows the packing of the molecules.

In the compound **3a** the C1/C2/C3/C4/C5/C6 cyclohexenone ring adopts half chair conformation in which C1 and C4 are deviated by 0.0691(2) and 0.6310(2). Similarly the C10/C11/C12/C13/C14/C15 cyclohexenone ring adopts boat conformation, in which C10 and C13 are deviated by 0.1397(2) and 0.6587(2). Both C4 and C13 atoms carry two methyl groups, lying above the respective mean plane.

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Compound name	За
CCDC No.	CCDC-1874715
Chemical formula	$C_{25}H_{325}O_{6}$
Formula weight	428.50
<i>T</i> [k]	100(2) K
Wavelength [Å]	0.71073 Å
Crystal system	Triclinic
Space group	<i>P</i> -1
<i>a</i> [Å]	9.0127(9) Å
b [Å]	9.6897(10) Å
c [Å]	13.9770(13) Å
α [°]	88.978(3)°
β	80.974(3)°
v	65.934(3)°
Volume	1099.27(19) A ³
Z. Density	2, 1.301 mg/m ³
Absorption coefficient	$0.092 \mathrm{mm^{-1}}$
F(000)	464
Crystal size	0.14 imes 0.17 imes 0.15mm
Theta range for data collection	2.51–25.00°
Limiting indices	-10 < h < 10, -11 < k < 11, -16 < < 16
Reflections collected/unique	13461/3882 [R(int) = 0.0779]
Completeness to theta	99.9%
Max. and min. transmission	0.9864 and 0.9855
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3882/0/288
Goodness-of-fit on F^2	0.930
Final R indices $[l > 2$ sigma (l)	$R_1 = 0.0580, wR_2 = 0.1005$
R indices (all data)	$R_1 = 0.1185, wR_2 = 0.1128$

Table 3. Crystal data and refinement parameters for the compound 3a.

Table 4. Non-bonded interactions and possible hydrogen bonds (Å) for compound 3a (D, donor; A, acceptor; H, hydrogen).

D–H […] A	D–H	H A	D A	D–H […] A
02–H2 […] 01	0.840	1.762	2.570	160.91
03–H3 […] 04	0.840	1.853	2.678	167.36
C16–H16B ··· O5 ⁽ⁱ⁾	0.980	2.581	3.493	154.91
C8–H8B···Cg ⁽ⁱⁱ⁾	0.980	2.69	3.370	136
C7–H7A ¹¹ O4 ⁽ⁱⁱⁱ⁾	0.980	2.760	3.536	152.08
C5–H5A ¹¹ O6 ^(iv)	0.990	2.625	3.589	164.66
C12–H12A···O1 ^(v)	0.9990	2.699	3.433	131.19

Symmetry codes: (i) -x + 1, -y, -z; (ii) -x, -y, -z; (iii) -x + 2, -y + 1, -z; (iv) x + 1, +y - 1, +z; (v) -x + 2, -y + 1, -z + 1.

The 3,4-dimethoxy phenyl ring is almost perpendicular to the cyclohexenone rings (C1/C2/C3/C4/C5/C6) and (C10/C11/C12/C13/C14/C15) making a dihedral angle of 74.19(8)° and 70.08(5)° respectively. The molecules in the crystal lattice are held together by pair of weak intramolecular O-H...O hydrogen bonds forming parallel layers to the, ab planes, forming inversion dimers. C-H...O and C-H...J intermolecular interactions are also observed. The hydroxyl and carbonyl oxygen atoms face each other and are oriented to allow the formation of the two intramolecular O-H...O hydrogen bonds which are typical of tetraketones due to their close proximity.

The atom O1 present in compound **3a** accepts proton from two different donors, O2 and C12 generating bifurcated bonds along 'c' axis. The crystal structure is further stabilized by C8–H8B... Cg interaction (Cg is the centroid of aryl ring C21/C22/C23/C18/C19/C20) with a distance of 2.759 Å.



Figure 2. ORTEP view of compound 3a.

4.2. Theoretical studies

4.2.1. Hirshfeld surface analysis

In order to study the intermolecular interactions in compound **3a**, the Hirshfeld surface (HS) analysis and related 2D finger plots were calculated using Crystal Explorer 17 [31] by submitting the crystallographic information file (cif) of compound **3a**. Surface features which are characteristic of different types of intermolecular interactions can be identified and these features can be visualized by color coding distances from the surface to the nearest atom exterior (d_e plots) or interior (d_i plots) to the surface [32–34]. The d_{norm} mapped on the Hirshfeld surfaces were generated with color scale in between -0.1489 au (blue) to 1.3286 au (red) respectively. The 2D fingerprint plots were displayed in the range of 0.4–2.6 D view with the d_e and d_i distance scales displayed on the graph axis. Further the shape index mapped Hirshfeld were also used to visualize different types of interactions. The intermolecular interactions in compound **3a** are visualized by mapping the Hirshfeld surface with different properties like d_e , d_{norm} , curvedness mapped, fragment patch mapped, and shape index [37] in Fig. 4.

In the Hirshfeld surface with the d_{norm} white color surface indicate the contacts with the distances equal to the sum of the van der Waals radii and the red and blue color indicate the distances shorter and longer than the van der Waals radii respectively.

All the 2D fingerprint plots of the compound **3a** are shown in Fig. 5. It clearly indicates that, in this molecule intermolecular interactions contributed by C^{...}H, O^{...}H, O^{...}O, H^{...}H, and C^{...}O, the maximum contribution are given by H^{...}H (59.7%) and O^{...}H (26.4%)



Figure 3. Packing of the compound 3a showing intramolecular O–H…O (a) and intermolecular C–H…O (b, c) and C–H… π (d) interactions.



Figure 4. d_{norm} mapped, curvedness mapped, fragment patch mapped and shape index mapped on Hirshfeld surface respectively of the compound **3a**.



Figure 5. Finger print plots of compound 3a.

Table 5. F	Percentage c	of Hirshfeld	finger	print	of the	compound	3a.
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С…Н	0…H	0…0	Н…Н	C…0
12.7%	26.4%	0.7%	59.7%	0.5%

	Table 6.	Comparison	of SCXRD	and DF1	bond	lengths	[Å]	of	compound	3a.
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	Distar	nce (Å)		Distar	ice (Å)
Atoms	SCXRD	DFT	Atoms	SCXRD	DFT
O(1)-C(2)	1.247(3)	1.24095	C(15)-C(14)	1.506(3)	1.51762
O(2)-C(11)	1.334(3)	1.32103	C(12)–C(13)	1.526(3)	1.53940
O(4)-C(15)	1.247(3)	1.24493			
O(5)-C(21)	1.371(3)	1.36217			
O(5)-C(25)	1.423(3)	1.41887	C(4)–C(8)	1.523(3)	1.53783
O(6)-C(20)	1.364(3)	1.36247	C(4)–C(7)	1.530(3)	1.54103
O(6)-C(24)	1.434(3)	1.41801	C(14)-C(13)	1.525(3)	1.53747
C(1)–C(9)	1.524(3)	1.53187	C(13)–C(17)	1.524(3)	1.53749
C(10)-C(15)	1.452(3)	1.44926			
C(10)-C(9)	1.514(3)	1.53010			
C(18)–C(23)	1.378(3)	1.38724			
C(18)–C(19)	1.403(3)	1.40630			
C(18)-C(9)	1.538(3)	1.54007			
C(21)-C(22)	1.371(3)	1.38729			
C(21)-C(20)	1.409(3)	1.41528			
C(3)–C(2)	1.506(3)	1.51990			
C(3)–C(4)	1.525(3)	1.53888			
C(19)-C(20)	1.384(3)	1.38916			
C(6)–C(5)	1.492(3)	1.50433			
C(13)–C(16)	1.533(3)	1.54178			
C(11)-C(12)	1.496(3)	1.50585			
C(22)-C(23)	1.390(3)	1.40079			

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		Angle (°)			Angle (°)		
Atoms		SCXRD	DFT	Atoms	SCXRD	DFT	
C(21)-O(5)-C(25)		115.28(19)	118.09262	C(20)-O(6)-C(24)	117.23(19)	118.52770	
C(6)–C(1)–C(2)		117.9(2)	118.15600	C(6)–C(1)–C(9)	121.3(2)	118.52770	
C(2)–C(1)–C(9)		120.7(2)	120.41526	C(11)–C(10)–C(15)	117.1(2)	118.04433	
C(11)–C(10)–C(9)		126.4(2)	125.89985	C(15)–C(10)–C(9)	116.3(2)	115.93086	
C(23)–C(18)–C(19)		117.7(2)	117.74304	C(23)–C(18)–C(9)	124.6(2)	122.57076	
C(19)-C(18)-C(9)		117.4(2)	119.28036	C(10)–C(9)–C(1)	115.28(19)	113.03982	
C(10)-C(9)-C(18)		115.2(2)	115.97611	C(1)–C(9)–C(18)	113.5(2)	114.74335	
C(1)-C(6)-C(5)		123.9(2)	119.67244	C(10)–C(11)–C(12)	123.5(2)	124.93294	
C(11)-C(12)-C(13)		113.3(2)	114.95060	C(3)-C(4)-C(7)	109.5(2)	110.77985	
C(3)-C(4)-C(5)	106.8(2)		107.62114				
C(19)-C(20)-C(21)	119.6(2)		119.67244				
O(5)-C(21)-C(20)		115.6(2)	116.09156				
C(2)-C(3)-C(4)		114.1(2)	115.85794				
C(20)-C(19)-C(18)		121.4(2)	121.85186				
O(6)-C(20)-C(19)	125.1(2)		124.80402				
O(6)-C(20)-C(21)		115.3(2)	115.52350				
O(3)-C(6)-C(1)		123.8(2)	124.47231				
O(3)-C(6)-C(5)		112.2(2)	111.69220				
O(2)-C(11)-C(12)		112.2(2)	111.74197				
C(21)-C(22)-C(23)		120.6(2)	120.95014				
C(18)-C(23)-C(22)	121.6(2)		120.19692				
O(1)-C(2)-C(1)		122.3(2)	122.13907				
C(15)-C(14)-C(13)		113.9(2)	115.06007				
C(1)-C(2)-C(3)		119.7(2)	119.99405				
C(10)-C(15)-C(14)		119.9(2)	120.22762				
C(8)-C(4)-C(5)		109.8(2)	109.57553				
C(8)-C(4)-C(7)		109.2(2)	109.57553				
C(5)-C(4)-C(7)		111.4(2)	110.44630				
O(4)-C(15)-C(10)		121.4(2)	121.90257				
O(4)-C(15)-C(14)	118.7(2)		117.79941				
C(17) - C(13) - C(12)		109.8(2)	109.47983				
C(17)-C(13)-C(16)		108.4(2)	108.79083				
C(12)-C(13)-C(16)		111.0(2)	110.87814				
C(14)-C(13)-C(12)		106.6(2)	107.30129				
C(14)-C(13)-C(16)		110.5(2)	110.45560				
C(22)-C(21)-C(20)		119.1(2)	118.60774				

Table 7.	Comparison	of SCXRD	and DFT	bond	angles	[°]	for	compound	3a.
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followed by C···H (12.7%), O···O (0.7%) and C···O (0.5%). The contribution of different atoms are listed in Table 5. The higher amount of H···H interaction in this compound shows that van der Waals interaction also plays a major role in the crystal packing.

4.2.2. Molecular geometry optimizations

The structure of the compound **3a** was optimized by DFT calculations using B3LYP method with 6-311 + G (d,p) basis set. The comparison of selected optimized geometrical parameters such as bond length, bond angles and torsion angles, with those parameters obtained from XRD studies are listed in Tables 6–8. The minor deviations observed between the theoretically calculated and experimentally determined values can be accounted for the differences in molecular environment between the crystalline phase and gas phase.

4.2.3. Frontier molecular orbital analysis

HOMO; highest occupied molecular orbital and LUMO; lowest unoccupied molecular orbital, are known as FMOs. The energy difference between the HOMO and LUMO

	Ang	gle (°)		Ang	Angle (°)		
Atoms	SCXRD	DFT	Atoms	SCXRD	DFT		
C(11)-C(10)-C(9)-C(1)	-80.5(3)	-83.64411	C(15)-C(10)-C(9)-C(1)	94.0(3)	92.19095		
C(11)-C(10)-C(9)-C(18)	54.7(3)	51.84836	C(15)-C(10)-C(9)-C(18)	-130.8(2)	-132.31658		
C(6)-C(1)-C(9)-C(10)	-93.1(3)	-91.85651	C(2)-C(1)-C(9)-C(10)	82.7(3)	83.42884		
C(6)-C(1)-C(9)-C(18)	130.9(2)	132.08233	C(2)-C(1)-C(9)-C(18)	-53.3(3)	-52.63231		
C(23)-C(18)-C(9)-C(10)	0.4(3)	16.63517	C(19)-C(18)-C(9)-C(10)	173.4(2)	-170.84614		
C(23)-C(18)-C(9)-C(1)	136.4(2)	151.37607	C(19)–C(18)–C(9)–C(1)	-50.5(3)	-36.10525		
C(25)-O(5)-C(21)-C(22)	-6.8(3)	-0.49784	C(25)-O(5)-C(21)-C(20)	172.6(2)	179.62237		
C(23)-C(18)-C(19)-C(20)	-0.9(4)	-1.06594	C(9)-C(18)-C(19)-C(20)	-174.4(2)	-173.94423		
C(24)-O(6)-C(20)-C(19)	-2.6(3)	0.37774	C(24)-O(6)-C(20)-C(21)	177.4(2)	-179.68963		
C(18)-C(19)-C(20)-O(6)	-179.9(2)	-179.87648	C(18)-C(19)-C(20)-C(21)	0.2(4)	0.19349		
O(5)-C(21)-C(20)-O(6)	0.3(3)	0.49604	C(22)-C(21)-C(20)-O(6)	179.8(2)	-179.39221		
O(5)-C(21)-C(20)-C(19)	-179.7(2)	-179.56763	C(22)-C(21)-C(20)-C(19)	-0.3(4)	0.54412		
C(2)-C(1)-C(6)-O(3)	-169.5(2)	-170.26664	C(9)-C(1)-C(6)-O(3)	6.4(4)	5.12208		
C(2)-C(1)-C(6)-C(5)	10.1(4)	8.15180	C(9)-C(1)-C(6)-C(5)	-174.0(2)	-176.45948		
C(15)-C(10)-C(11)-O(2)	-168.0(2)	-169.96904	C(9)–C(10)–C(11)–O(2)	6.5(4)	5.78689		
C(15)-C(10)-C(11)-C(12)	13.5(3)	9.50414	C(9)-C(10)-C(11)-C(12)	-172.0(2)	-174.73993		
O(5)-C(21)-C(22)-C(23)	-179.6(2)	179.72859	C(20)-C(21)-C(22)-C(23)	1.0(4)	-0.39438		
C(19)-C(18)-C(23)-C(22)	1.6(4)	1.21676	C(9)-C(18)-C(23)-C(22)	174.6(2)	173.84431		
C(21)-C(22)-C(23)-C(18)	-1.7(4)	-0.50811	C(6)-C(1)-C(2)-O(1)	172.9(2)	169.13508		
C(9)–C(1)–C(2)–O(1)	-3.0(3)	-6.29445	C(6)-C(1)-C(2)-C(3)	-3.3(3)	-7.69876		
C(9)-C(1)-C(2)-C(3)	-179.2(2)	176.87170	C(4)-C(3)-C(2)-C(1)	-30.1(3)	-21.82891		
C(4)-C(3)-C(2)-O(1)	153.5(2)	161.20159	C(11)-C(10)-C(15)-O(4)	165.2(2)	169.52553		
C(9)–C(10)–C(15)–O(4)	-9.9(3)	-6.65239	C(11)-C(10)-C(15)-C(14)	-12.4(3)	-7.35556		
C(9)–C(10)–C(15)–C(14)	172.6(2)	176.46652	O(2)-C(11)-C(12)-C(13)	-158.3(2)	-160.75417		
C(10)-C(11)-C(12)-C(13)	20.4(3)	19.71080	O(3)-C(6)-C(5)-C(4)	-163.5(2)	-160.46891		
C(1)-C(6)-C(5)-C(4)	17.0(4)	20.93426	C(2)-C(3)-C(4)-C(8)	172.0(2)	166.20677		
C(2)-C(3)-C(4)-C(5)	52.9(3)	47.04114	C(2)-C(3)-C(4)-C(7)	-67.9(3)	-73.79303		
C(6)-C(5)-C(4)-C(8)	-165.8(2)	-165.58396	C(6)-C(5)-C(4)-C(3)	-46.5(3)	-46.32319		
C(6)-C(5)-C(4)-C(7)	73.1(3)	74.72029	O(4)-C(15)-C(14)-C(13)	160.0(2)	159.12895		
C(10)-C(15)-C(14)-C(13)	-22.4(3)	-23.86419	C(15)-C(14)-C(13)-C(17)	171.8(2)	167.94693		
C(15)-C(14)-C(13)-C(12)	52.5(3)	48.97339	C(15)–C(14)–C(13)–C(16)	-68.2(3)	-71.99587		
C(11)-C(12)-C(13)-C(17)	-171.3(2)	-166.27222	C(11)-C(12)-C(13)-C(14)	-51.6(3)	-47.01427		

Table 8. Comparison of SCXRD and DFT calculated torsion angles [°] for compound 3a.

orbitals is called the energy gap (E_g). The calculated HOMO and LUMO energies for compound **3a** in Fig. 6 is found to be -5.571 eV and -1.624 eV respectively and energy gap ($E_g = E_{\text{LUMO}} \cdot E_{\text{HOMO}}$) is 3.947 eV. This large energy gap value in the compound **3a** indicates high stability and low reactivity [38]. The importance of the FMOs is in determining the electronic properties, optical properties, and chemical reactivity's. The energy of the highest occupied molecular orbital (HOMO) is related to the ionization potential, while the energy of the lowest unoccupied molecular orbital (LUMO) is related to the electronic affinity.

The global reactivity parameters related to frontier molecular orbital energies are chemical hardness ($\eta = 1.973 \text{ eV}$), electronegativity ($\chi = 3.597 \text{ eV}$), electronic chemical potential ($\mu = -3.597 \text{ eV}$), global electrophilicity index ($\omega = 3.278 \text{ eV}$). Table 9 which were calculated from HOMO–LUMO energy values [39].

4.2.4. Atomic charge analysis

The Mulliken charge distributions of the compound **3a** have been calculated using 6-311 + G (d,p) level shown in Fig. 7. In compound **3a**, the magnitude of the carbon Mulliken charges, is found to be either positive or negative ranging from -1.188 to



Figure 6. HOMO–LUMO orbitals of title compound 3a.

Table 9. The energy values of global reactivity descriptors.

Parameter	Value (eV)
ELUMO	-1.624
EHOMO	-5.571
ΔE	3.947
Chemical hardness (η)	1.973
Electronegativity (χ)	3.597
Chemical potential (µ)	-3.597
Chemical softness (s)	0.253
Global electrophilicity index (ω)	3.278





1.521. The highest positive charge is over carbon (C1 = 1.521) atom. Among all the protons which carry positive charge the highest positively charged hydrogen atoms are H2 (0.389) and H3 (0.35), while all oxygen atoms have a negative charge.



Figure 8. MEP surface of title compound 3a.

4.2.5. Molecular electrostatic potential analysis

The molecular electrostatic potential (MEP) analysis can be regarded as a powerful tool for identifying the possible interaction sites around a molecule. One of the most interesting features of quantum chemistry is the ability to explain the reactivity of compounds under investigation. It determines the reactivity of a chemical system by predicting electrophilic as well as nucleophilic sites in target molecules. The computed MEP using 6-311 + G (d,p) level of DFT is shown in Fig. 8. The MEP surface allows us to visualize the various regions of a molecule. The charge distribution helps to determine the molecules interaction and the nature of the chemical bond. The positive area of the MEP is a nucleophilic site, while the negative region is associated with an electrophilic site. Figure 8 shows the negative charges are more and they are concentrated around the oxygen atom. The color code of the map is in the range between -5.939×10^{-2} a.u. (deepest red) and 5.939×10^{-2} a.u. (deepest blue) in the maps, the most negative region on the MEP surface of the title compound is associated with the lone-pairs of the oxygen atom.

5. Conclusion

In conclusion, application of ultrasound results in significant benefits such as intensified processing, low level of waste generation, inherently safe operation, material and energy saving as well as increase in productivity, all of which confirm the greener processing based on the use of ultrasound.

We have developed an environmentally benign and green method using less harmful solvents such as ethanol-water system in the presence of Bronsted acid catalyst such as

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boric acid for the syntheses of tetraketones. Further studies in our laboratory are underway to develop multicomponent reactions in milder reaction medium.

The single crystal X-ray studies revealed that the title compound is stabilized by a pair of intramolecular O-H···O and intermolecular C-H···O and C-H··· π interactions. As for the calculated DFT, by B3LYP method it shows good agreement with the experimental results. The three-dimensional d_{norm} and 2D fingerprint plots from Hirshfeld surfaces analysis were extensively studied to understand the intermolecular interactions. The Hirshfeld surface analysis disclosed that maximum interactions, contributed for crystal packing was from H···H (59.7%) and O···H (26.4%). The correlation coefficient between the bond lengths and bond angles of experimental and theoretical values showed that the structure obtained by the single crystal XRD is well agreeable with the optimized structure. The MEP plots revealed the possible reactions sites of the molecule. The Mulliken atomic charges were also analyzed for the nucleophilic and electrophilic regions on the molecular surface. The HOMO-LUMO large energy gap value of the compound indicates high stability and low reactivity suggesting a good stability of the compound **3a**.

6. Supplementary data

Supplementary crystallographic data for this article in CIF format are available at the Electronic Supplementary Publication from Cambridge Crystallographic Data Center (CCDC 1874715). http://www.ccdc.cam.ac.uk/conts/retrieving.html, from the Cambridge Crystallographic Data Center, 12 Union Rood, Cambridge CB2 1EZ, UK (Fax: (international): +44 1223/336 033; email: deposit @ ccdc.cam.ac.uk).

References

- [1] M. B. Gawande et al., Chem. Soc. Rev. 42 (12), 5522 (2013). doi:10.1039/c3cs60025d
- [2] P. T. Anastas and T. Williamson, *Green Chemistry Frontiers in Benign Chemical Synthesis* and Process (Oxford University Press, Oxford, UK, 1998), p. 360.
- [3] P. A. Grieco, Organic Synthesis in Water (Thomson Science, London, 1998), p. 1.
- [4] Z. Ren et al., Synth. Commun. 32 (13), 1947 (2002). doi:10.1081/SCC-120004844
- [5] G. M. Maharvi et al., J. Enzyme Inhibit. Med. Chem. 23 (1), 62 (2008). doi:10.1080/ 14756360701408754
- [6] J. P. Poupelin et al., Eur. J. Med. 13, 67 (1978).
- [7] R. M. Ion, Progr. Catalysis 2, 55 (1997).
- [8] R. M. Ion et al., Acta Biochim. Pol. 45 (3), 833 (1998). doi:10.18388/abp.1998_4279
- [9] K. Vorlander, Justus Liebigs Ann. Chem. Am. Foreign J. 309, 380 (1899).
- [10] T. J. Mason and D. Peters, Practical Sonochemistry (Ellis Horwood, New York, 1991).
- [11] T. J. Mason, Ultrason. Sonochem. 14 (4), 476 (2007).
- [12] P. Abbott et al., Chem. Commun. (1), 70 (2003). doi:10.1039/b210714g
- [13] G. Cravotto et al., Eur. J. Org. Chem. 2003 (22), 4438 (2003). doi:10.1002/ejoc.200300369
- [14] B. A. Marco et al., J. Chem. Crystallogr. 29, 75 (1999).
- [15] K. M. Khan et al., Bioorg. Med. Chem. 14 (2), 344 (2006). doi:10.1016/j.bmc.2005.08.029
- [16] D. B. Ramachary and M. J. Kishor, J. Org. Chem. 72 (14), 5056 (2007). doi:10.1021/ jo070277i
- [17] D. Prasad, A. Preetam, and M. Nath, C. R. Chim. 15 (8), 675 (2012). doi:10.1016/j.crci. 2012.05.018
- [18] J. J. Wang et al., Green Chem. 12 (2), 216 (2010). doi:10.1039/B913816A

- [19] G. Kaupp, M. R. Naimi-Jamal, and J. Schmeyers, *Tetrahedron* 59 (21), 3753 (2003). doi:10. 1016/S0040-4020(03)00554-4
- [20] Bruker.SMART, SAINT-Plus, and SADABS. Bruker Axs Inc., Madison, Wisconsin, USA, 1998.
- [21] G. M. Sheldrick, Acta Crystallogr. A Found. Crystallogr. 64 (Pt 1), 112 (2008). doi:10.1107/ S0108767307043930
- [22] M. Nardelli, Acta Crystallogr. C Cryst. Struct. Commun. 39 (8), 1141 (1983). doi:10.1107/ S0108270183007696
- [23] L. J. Farrugia, J. Appl. Crystallogr. 30 (5), 565 (1997). doi:10.1107/S0021889897003117
- [24] K. Brandenburg and H. Putz, Crystal Impact (GbR, Bonn, Germany, 2005).
- [25] M. J. Frisch et al., Gaussian 16 Revision B.01 (Gaussian Inc., Wallingford, CT, 2016).
- [26] K. T. A. Dennington and J. M. Millam, GaussView, Version 6 (Semichem Inc., Shawnee Mission, KS, 2016).
- [27] A. D. Becke, J. Chem. Phys. 96 (3), 2155 (1992). doi:10.1063/1.462066
- [28] A. D. Becke, J. Chem. Phys. 98 (7), 5648 (1993). doi:10.1063/1.464913
- [29] C. Lee, W. Yang, and R. G. Parr, Phys. Rev. B Condens. Matter. 37 (2), 785 (1988). doi:10. 1103/physrevb.37.785
- [30] T. Koopmans, *Physica* 1 (1-6), 104 (1934). doi:10.1016/S0031-8914(34)90011-2
- [31] M. J. Turner et al., 2017. CrystalExplorer17.
- [32] M. A. Spackman and J. J. McKinnon, Cryst. Eng. Commun. 4 (66), 378 (2002). doi:10. 1039/B203191B
- [33] M. A. Spackman and D. Jayatilaka, Cryst. Eng. Commun. 11 (1), 19 (2009). doi:10.1039/ B818330A
- [34] J. J. McKinnon, M. A. Spackman, and A. S. Mitchell, Acta Crystallogr. B 60 (Pt 6), 627 (2004). doi:10.1107/S0108768104020300
- [35] T.-W. Chung et al., Org. Lett. 17 (21), 5368 (2015). doi:10.1021/acs.orglett.5b02705
- [36] E. C. Horning and M. G. Horning, J. Org. Chem. 11, 95 (1946). doi:10.1021/jo01171a014
- [37] J. J. McKinnon, D. Jayatilaka, and M. A. Spackman, Chem. Commun. 3814 (37), 3814 (2007). doi:10.1039/b704980c
- [38] J. Aihara, Chem. Acc. 102 (1-6), 134 (1999). doi:10.1007/s002140050483
- [39] P. K. Bayannavar et al., J. Mol. Struct. 1179, 809 (2019). doi:10.1016/j.molstruc.2018.11. 060