

Communication

Ethyl 2,6-Dimethoxybenzoate: Synthesis, Spectroscopic and X-ray Crystallographic Analysis

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Abstract: The acid catalyzed esterification of 2,6-dimethoxybenzoic acid (**1**) in the presence of absolute ethanol afforded ethyl 2, 6-dimethoxybenzoate (**2**). The structure of the resulting compound was supported by spectroscopic data and unambiguously confirmed by single crystal X-ray diffraction studies. The title compound crystallized in the triclinic space group $P\bar{1}$ with unit cell parameters $a = 8.5518(3)$ Å, $b = 10.8826(8)$ Å, $c = 11.9939(6)$ Å, $\alpha = 101.273(5)^\circ$, $\beta = 98.287(3)^\circ$, $\gamma = 94.092(4)^\circ$, $V = 1077.54(10)$ Å³, $Z = 4$, $D_c = 1.296$ Mg/m³, $F(000) = 448$ and $\mu = 0.098$ mm⁻¹. Compound (**2**) crystallizes with two molecules in the asymmetric unit with similar conformations.

Keywords: esterification; ethyl 2,6-dimethoxybenzoate; spectroscopic data; crystal structure

1. Introduction

Ester derivatives are imperative intermediates in organic synthesis, which have been employed in various areas including medicinal chemistry [1–3], chiral sources [4–6], polymer materials [7,8] and for the synthesis of a variety of biologically important heterocycles including 1,2,4-triazoles, 1,3,4-thiadiazoles [9] and 1,3,4-oxadiazoles [10]. The benzoate derivatives have also been reported to show

a strong antifeedant effect on the pine weevil [11] and corrosion inhibitive properties for different metals such as aluminum, zinc and copper [12].

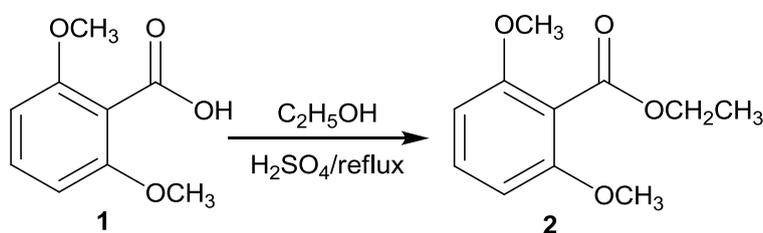
Esters of substituted benzoic acids are also used as anti-thrombotic agents [13] and have attracted substantial attention in medicinal research due to their antimycotic activities and cytotoxicity against a wide variety of tumor cell lines [14]. Furthermore, these derivatives are applicable as emulsifiers for foodstuffs, personal care products, and medical supplies and possess some antimicrobial and insecticidal activities [15]. Literature investigations revealed that similar benzoate derivatives have been reported by Qadeer [16], Saleem [17] and Kumar *et al.* [3].

In the present study, we report the synthesis and X-ray crystal structure of ethyl 2,6-dimethoxybenzoate.

2. Results and Discussion

The reaction sequence leading to the formation of the title compound is outlined in Figure 1. By adopting the procedure of [18], 2,6-dimethoxybenzoic acid (**1**) was transformed to the corresponding ethyl 2,6-dimethoxybenzoate (**2**) resulting in excellent yield.

Figure 1. The synthesis of title compound **2**.



In the IR spectrum, Compound (**2**) showed the characteristic stretching band for C=O (ester) at 1729 cm⁻¹ indicating the formation of the required product. Similarly, disappearance of the broad COOH peak in the range 3400–2400 cm⁻¹ and C=O (acid) stretching frequency in the range 1720–1700 cm⁻¹ also indicated the formation of ester (**2**). Moreover, the appearance of stretching bands for CH₂ and CH₃ at 2965 and 2843 cm⁻¹, respectively, also indicated the formation of the title compound. The ¹H-NMR spectrum showed characteristic signals at 4.40 and 1.38 ppm for methylene and methyl protons, respectively, in addition to those due to aromatic protons in the range of 7.29–6.57 ppm. In the ¹³C-NMR spectrum, the characteristic signal for C=O appeared at 166.7 ppm along with aromatic signals at their respective chemical shifts. In addition, the appearance of two signals for methylene and methyl protons at 56.0 and 41.3 ppm, respectively, also confirmed the product. The title compound was further confirmed by mass spectrometry and microanalysis.

The molecular structure was established by single crystal X-ray diffraction studies. Compound (**2**) crystallizes with two molecules in the asymmetric unit, both molecules adopt similar conformations, however, the ethoxy group in molecule one (left in Figure 2) is disordered over two closely related conformations with refined occupancies close to 50%. For this reason, discussion of the structural parameters will be restricted to the ordered molecule. A thermal ellipsoid plot at 20% probability level for compound (**2**) is presented in Figure 2. The crystal and instrumental parameters used in the unit cell

determination, the data collection, and structure refinement parameters are presented in the experimental section [19] while selected bond distances and angles are shown in Table 1.

Figure 2. Thermal ellipsoid plot of the two molecules of title compound **2**. The ethoxy group in molecule one (left) has refined occupancies of 50% over the two sites. The ellipsoids are at the 20% probability level.

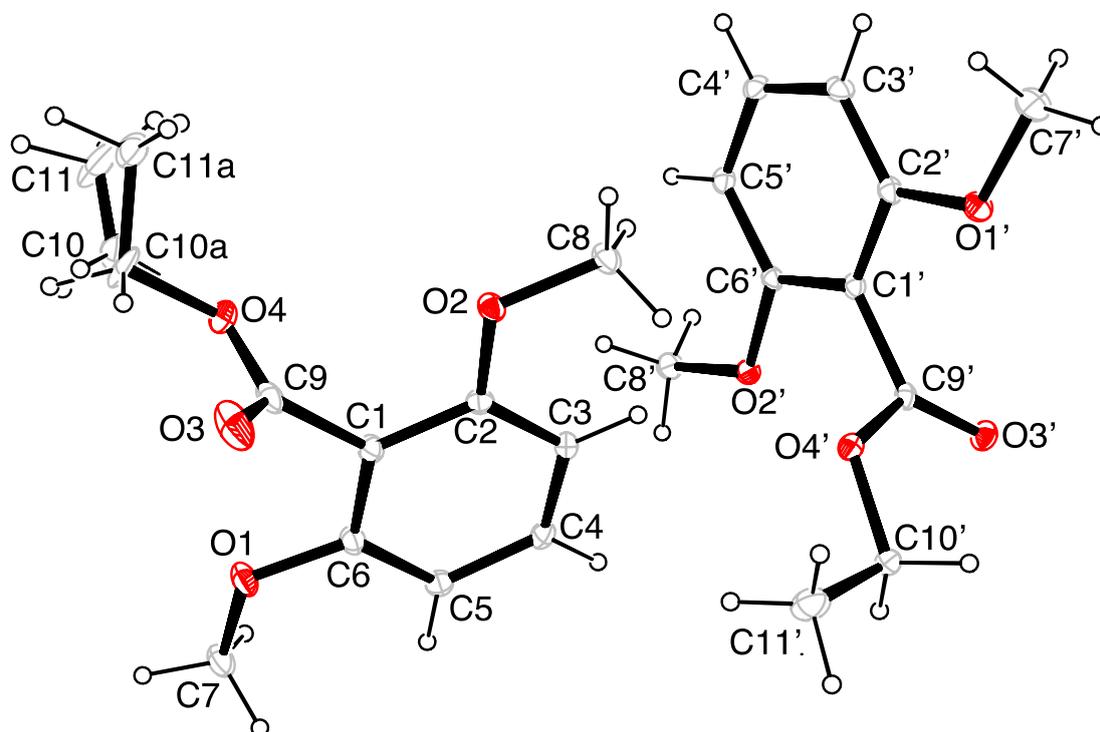


Table 1. Selected bond lengths [Å] and angles [°] in compound **2**.

Atoms	Bond length	Atoms	Bond angle
O(2')-C(6')	1.367(2)	C(6')-O(2')-C(8')	116.91(14)
O(2')-C(8')	1.429(2)	C(2')-O(1')-C(7')	116.82(16)
O(3')-C(9')	1.202(2)	C(9')-O(4')-C(10')	117.21(14)
O(1')-C(2')	1.362(2)	C(6)-O(2)-C(8)	117.52(15)
O(1')-C(7')	1.432(2)	O(2')-C(6')-C(1')	115.06(16)
O(4')-C(9')	1.336(2)	O(1')-C(2')-C(3')	125.07(17)
O(4')-C(10')	1.456(2)	O(2')-C(6')-C(5')	124.77(17)
O(1)-C(6)	1.368(2)	O(4')-C(9')-C(1')	109.96(15)
O(4)-C(10A)	1.504(4)	O(4')-C(10')-C(11')	106.46(16)
C(10')-C(11')	1.497(3)	O(3)-C(9)-O(4)	124.5(2)
C(10A)-C(11A)	1.214(5)	C(11A)-C(10A)-O(4)	120.2(5)

The presence of the two methoxy substituents ortho to the ethyl ester group forces this substituent to adopt a conformation which is essentially orthogonal to the aromatic ring ($O(3')-C(9')-C(1')-C(6') = 88.6(2)^\circ$). This electronically less favoured conformation prevents any resonance interaction between

the carbonyl group and the aromatic ring. As a result the C1-C9 bond distance of 1.497(2) Å is at the longer side of all the Ar-CO₂Et bond distances 1.485(8) Å obtained from the Cambridge Crystallographic database [20] for ethyl benzoate derivatives (organic molecules only) in which the carbonyl group is co-planar (within $\pm 20^\circ$) with the aromatic ring (204 hits with R factors < 5%). However, there is close agreement between the C1-C9 bond distance with the corresponding distance (1.498 (2) Å) observed for the methyl ester derivative [19] which exists in a similar conformation to that observed for compound (2). This shorter bond distance is consistent with the expected structural effect associated with the resonance interaction of the carbonyl group with the aromatic ring.

Interestingly, if a search is made of those ethyl esters in which the carbonyl group is constrained to be close to orthogonal with the ring ($90 \pm 20^\circ$), (8 hits with R factors < 5%) then the mean Ar-C bond distance increases to 1.508 Å. The two methoxy substituents are co-planar with the aromatic ring, this allows for delocalization of the oxygen *p*-type lone pair electrons with the aromatic ring, the Ar-OCH₃ bond distances for molecule two are 1.362 (2) and 1.367 (2) Å, respectively, which compares with 1.369 Å, the mean value from the Cambridge Crystallographic database (Search fragment; CH₃O-Ar, 10,022 hits with R factors < 5%). If a subset of this hit list is selected having the methoxy orthogonal to the aromatic ring ($90 \pm 20^\circ$), then the mean Ar-OCH₃ distance increases to 1.381 Å, demonstrating the bond-shortening effect of the lone pair delocalization with the aromatic ring.

The crystal packing of the two molecules of compound (2), is stabilized by a combination of dipole-dipole attraction, CH- π and weak CH...O interactions as presented in Table 2. There is no evidence for π - π stacking.

Table 2. Intermolecular interactions in compound 2.

C-H... π interactions	C-H...O interactions
H7B...C4' 2.856 (<i>x</i> , <i>y</i> , <i>I</i> + <i>z</i>)	H8b...O2 (<i>I</i> - <i>x</i> , - <i>y</i> , 2 - <i>z</i>) 2.620 Å
H7B...C5' 2.862	H4'...O3' (<i>I</i> + <i>x</i> , <i>y</i> , <i>z</i>) 2.680 Å
H3...C6' 2.888 Å	H7'1...O3 (<i>x</i> , <i>y</i> , <i>z</i> - <i>I</i>) 2.547 Å
H4'...C5 (<i>I</i> - <i>x</i> , <i>I</i> - <i>y</i> , 2 - <i>z</i>) 2.881 Å	H7 2...O1 (- <i>x</i> , - <i>y</i> , <i>I</i> - <i>z</i>) 2.654 Å
	H5...O3' (- <i>x</i> , <i>I</i> - <i>y</i> , 2 - <i>z</i>) 2.498 Å

3. Experimental Section

3.1. General

Proton (¹H) and carbon (¹³C) nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AV-300 spectrometer at 300 and 75 MHz, respectively. Spectra were measured in deuteriochloroform (CDCl₃) solution using residual solvent peak as the reference and coupling constants were determined in Hertz. Infrared spectrum was recorded on a Bruker Optics Alpha FTIR Spectrophotometer. Melting point was determined on a Sanyo Gallenkamp melting point apparatus in open capillary and remains uncorrected. Analytical thin-layer chromatography was carried out with Merck silica gel 60 F₂₅₄ aluminum backed sheets. Mass Spectrum was recorded on a Finnigan

MAT-311A (Germany) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed on a Carlo Erba Strumentazione-Mod-1106 Italy.

3.2. General Procedure for the Synthesis of Ethyl 2, 6-Dimethoxybenzoate (2)

Ethyl 2,6-dimethoxybenzoate (**2**) was synthesized by refluxing 2,6-dimethoxybenzoic acid (**1**) (0.01 mol) with absolute ethanol (25 mL) in the presence of a catalytic amount of sulfuric acid [18]. The reaction was monitored by thin layer chromatography. After completion of the reaction, the excess solvent was removed under reduced pressure and the resulting oil was poured into water. The aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with dilute solution of sodium carbonate to remove unreacted acid. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed on a rotary evaporator to afford the ester as white crystals (**2**).

Yield: 90% (1.89 g); mp 129–130 °C; R_f : 0.72 (petroleum ether : ethyl acetate, 8:2); IR (neat, cm^{-1}): 3065 ($\text{C}_{\text{sp}2}\text{-H}$), 2965, 2843 ($\text{C}_{\text{sp}3}\text{-H}$), 1729 (C=O), 1581, 1498 (C=C_{Ar}), 1228 (C-O); ^1H NMR (300 MHz, CDCl_3): δ 7.29 (d, 1H, $^3J = 8.4$ Hz, Ar-H), 6.57 (dd, 2H, $^3J = 8.4$ Hz, $^4J = 2.4$ Hz, Ar-H), 4.40 (q, 2H, $^3J = 7.2$ Hz, OCH_2), 3.82 (s, 6H, 2 × OCH_3), 1.38 (t, 3H, $^3J = 7.2$ Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3): δ 166.7, 157.2, 131.0, 113.3, 103.9, 61.3, 56.0, 14.3. EIMS: m/z 210 [M^+], 195, 181, 179, 165, 137, 45, 29, 15. Elemental analysis calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_4$: C, 62.85; H, 6.71. Found: C, 62.64; H, 6.49.

3.3. Data Collection and Structure Solution

A suitable crystal of ethyl 2,6-dimethoxybenzoate (**2**) having dimensions of 0.6 × 0.5 × 0.3 mm was selected and all the reflection data were collected on an Oxford SuperNova CCD diffractometer using Mo-K α ($\lambda = 0.71073$ Å) radiation at 130 K. The structure was solved by direct methods and refined by full-matrix least squares using SHELX-97 [21].

Crystal Data for 2. $\text{C}_{11}\text{H}_{14}\text{O}_4$, $M = 210.22$, crystal size, 0.6 × 0.5 × 0.3 mm. Triclinic, $P \bar{1}$, $a = 8.5518$ (3), $b = 10.8826$ (8), $c = 11.9939$ (6) Å, $\alpha = 101.273$ (5)°, $\beta = 98.287$ (3)°, $\gamma = 94.092$ (4)°, $V = 1077.54$ (10) Å³, $Z = 4$, $F(000) = 448$, $T = 130$ (2) K, $\rho_{\text{calc}} = 1.296$ mg/m³, $\mu = 0.098$ mm⁻¹, 7807 reflections measured, $R_{\text{int}} = 0.0202$, R indices [$I > 2\sigma(I)$]: $R1 = 0.0447$, $wR2 = 0.1143$, [all data] $R1 = 0.0545$, $wR2 = 0.1220$, Goodness-of-fit on $F^2 = 1.045$, data / restraints / parameters = 3782 / 0 / 298, wavelength = 0.7107 Å, max. and min. transmission = 1.00000 and 0.72479, extinction coefficient = 0.025(3), largest diff. peak and hole 0.428 and -0.391 e Å⁻³. CSD deposition number: CCDC 869822. CCDC 869822 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4. Conclusions

Synthesis, spectroscopic characterization and the X-ray crystal and molecular structure of ethyl 2,6-dimethoxybenzoate, have been described. The reaction offers convenient, mild conditions and good yield.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

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