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AN EFFICIENT $FeSO_4$ MEDIATED SYNTHESIS OF METHYL-4-(ETHOXYMETHYL)-BENZOATE AND BASIC CONFORMATIONAL ANALYSIS OF THE SAME USING COMPUTATIONAL TOOLS

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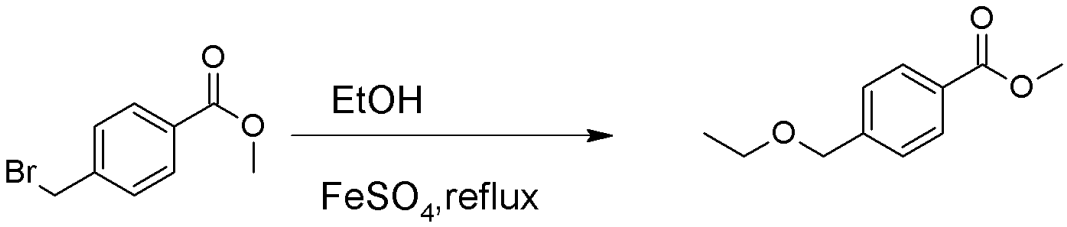
Graphical ABSTRACT:



ABSTRACT. The synthesis of Methyl-4-(ethoxymethyl)-benzoate from Methyl 4-(Bromomethyl) benzoate and ethyl alcohol using $FeSO_4$ as a recoverable and reusable mediator has been described without use of base and cosolvent under mild conditions and conformational analysis of the synthesized compound has been performed by computational tools.

Keywords: Methyl-4-(ethoxymethyl)-benzoate; methyl 4-(Bromomethyl) benzoate; ethyl alcohol; $FeSO_4$, conformational analysis

INTRODUCTION

Methyl-4-(ethoxymethyl)-benzoate is a substituted benzyl ether. Benzyl and substituted benzyl ethers are the most versatile protecting groups.[1, 2] The synthesis of benzyl alkyl ethers include Williamson ether synthesis under basic or acidic conditions using trichloroacetimidates [3] and benzyloxypyridinium triflates with alcohol in the presence of additives. [4] The literature survey evinces that only a few reports have been published for the

synthesis of substituted benzyl ethers like Methyl-4-(ethoxymethyl)-benzoate without base and additives. [5] Herein, I report the synthesis of particular benzyl alkyl ether that is Methyl-4-(ethoxymethyl)-benzoate from Methyl 4-(Bromomethyl) benzoate and alcohols using ferrous sulphate as a mediator without base and cosolvent using the procedure mentioned by JOSHI and ADIMURTHY [6].

In literature (WO/2007/126043) Methyl-4-(ethoxymethyl)-benzoate was prepared from methyl 4-(hydroxymethyl) benzoate with the reaction with EtI, t-BuOK, DMF.In this paper, preparation of Methyl-4-(ethoxymethyl)-benzoate was done with reaction between Methyl 4-(Bromomethyl) benzoate and ethyl alcohol using $FeSO_4$.

SYNTHESIS OF METHYL-4-(ETHOXYMETHYL)-BENZOATE (Fig. 1)

A mixture of Methyl 4-(Bromomethyl) benzoate (CAS#: 2417-72-3) (0.458 g, 2.0 mmol) and $FeSO_4$, $7H_2O$ (2.0 mmol, 0.556 gm.) were refluxed (magnetic stirrer is used) in ethanol (25.0 mL) at 78^0C for a period of 20 hours; progress of the reaction was monitored by thin-layer chromatography (TLC). The TLC was monitored by TLC Silica Gel 60 F_{254} under UV light. After complete disappearance of benzyl bromide, the reaction mixture was cooled to room temperature (25^0C), $FeSO_4$ was removed by filtration, and the residue was washed with 10mL of cold ethanol.

The characteristic red colour crude product was dried out by RotaVap and Vacuum pump.

The ethanol was stripped out, and the residue left out was purified by column chromatography on silica gel (100–200 mesh) to obtain the pure product as colorless liquid which is **Methyl-4-(ethoxymethyl)-benzoate.**

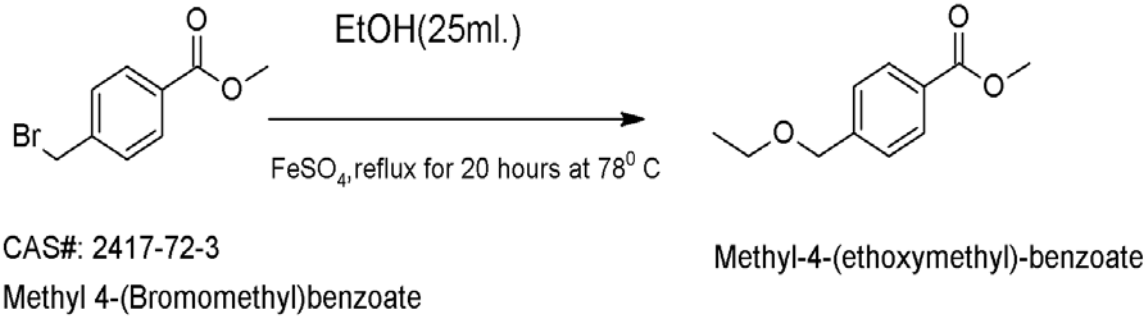


Fig. 1. - Synthesis scheme for Methyl-4-(ethoxymethyl)-benzoate.

EXPERIMENTAL

^{1}H spectra were recorded on a spectrometer operating at 500MHz in $CDCl_3$ unless otherwise stated. Column chromatography for purification was carried out on silica gel (100–200 mesh). Analytical thin-layer chromatography (TLC) was performed on an Aluchrosep silica gel 60/F_{254} plate under UV light. Mass spectroscopy of the sample was recorded on WATERS-Q-Tof Premier-HAB213 micro electrospray ionization (ESI) +ve mode.

Spectral data of the compound Methyl-4-(ethoxymethyl)-benzoate:

^{1}H NMR 500MHz($CDCl_3$): d(ppm) 1.235 (1, 3H, t, J=6.997), 3.815 (2, 3H), 7.331 (4, 1H, ddd, J=8.498, J=3.530, J=1.341), 7.324 (5, 1H, ddd, J=8.490, J=3.132, J=1.341), 7.924 (6, 1H, ddd, J=8.495, J=3.132, J=0.000), 7.924 (7, 1H, ddd, J=8.490, J=3.530,J=0.000),3.447(8,2H,q,J=6.997),4.548(9,2H);MS(ESI)($C_{11}H_{14}O_9$)=predicted[$M+H^+$]=195.1015,observed=195.1029,predicted[$M+Na^+$]=217.08341,observed =217.0851

COMPUTATIONAL METHOD

Computational conformational analysis and geometry optimization study of Methyl-4-(ethoxymethyl)-benzoate was performed on a window based computer using Argus lab [7] and ACD Lab Chem Sketch software's [8]. The Methyl-4 (ethoxymethyl)-benzoate was used to determine the 3D structure of the molecule (Fig. 7). The Methyl-4-(ethoxymethyl)-benzoate structure was generated by ArgusLab 4.0.1 and geometry optimization was performed with the semi-empirical RHF/ Austin Model 1(AM1) parameterization (DEWAR *et al*., 1985) [9].

The minimum potential energy is calculated by using geometry convergence function in Argus lab software. In order to determine the allowed conformation the contact distance between the atoms in adjacent residues is examined using criteria for minimum Vander Waal contact distance (SIMONS *et al*., 1983) [10].

Surfaces created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potentials (ESP) spin densities and generated the grid data used to make molecular orbital surfaces and visualized the molecular orbital (Fig. 4, 5) and making an electro static potential mapped and electron density surface (Fig. 6). The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map.

The final geometrical energy and SCF energy was found to be -59092.0491 kcal/mol as calculated by RHF/AM1 method performed by ArgusLab 4.0.1 suite.

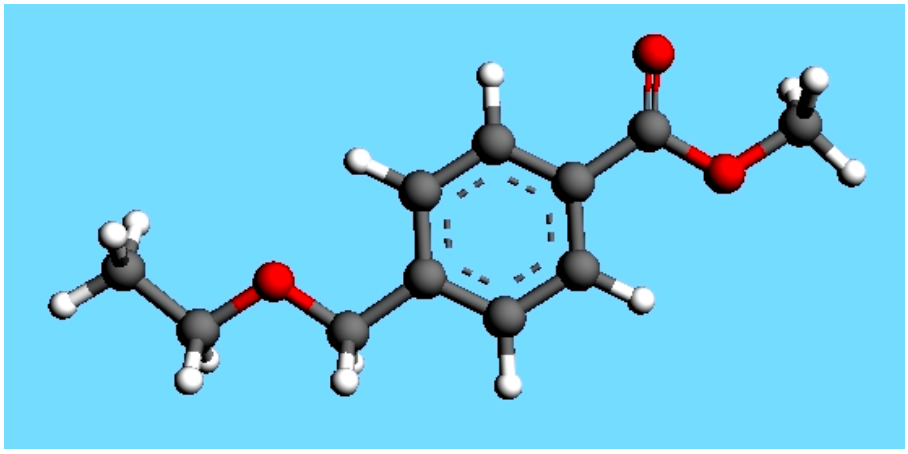


Fig. 2. - Perspective view and active conformation of Methyl-4-(ethoxymethyl)-benzoate as optimized by ArgusLab 4.0.1 software.

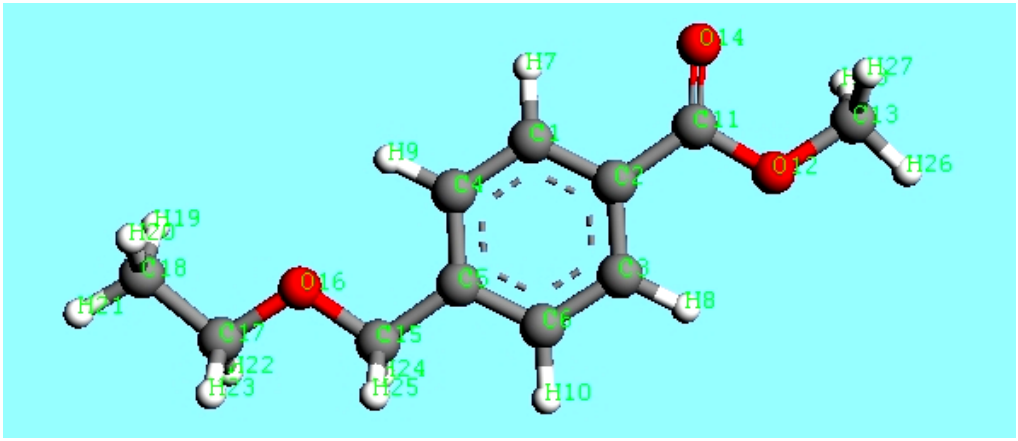


Fig. 3. - Methyl-4-(ethoxymethyl)-benzoate molecule with labelled atoms.

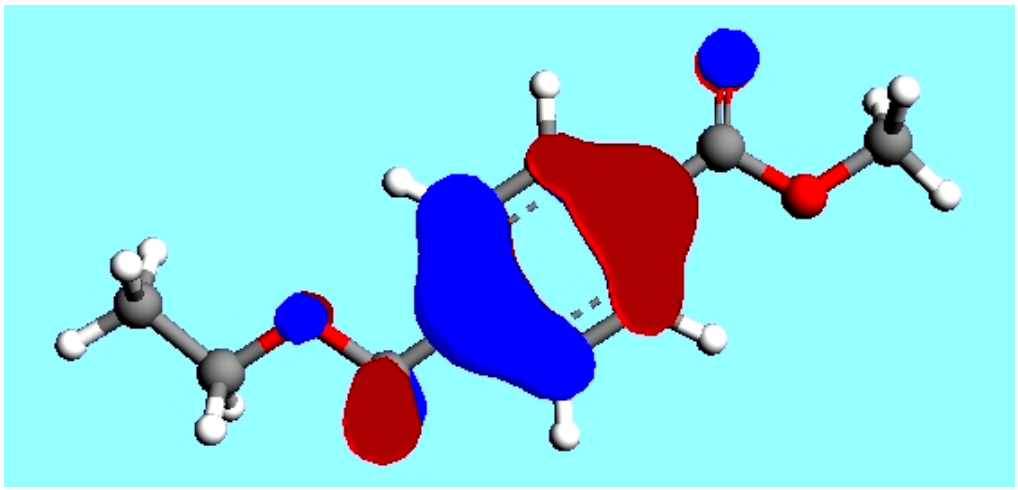


Fig. 4. - HOMO (Highest Occupied Molecular Orbitals) of Methyl-4-(ethoxymethyl)-benzoate as visualised by ArgusLab 4.0.1 , blue shows positive and red shows negative charged MO s.

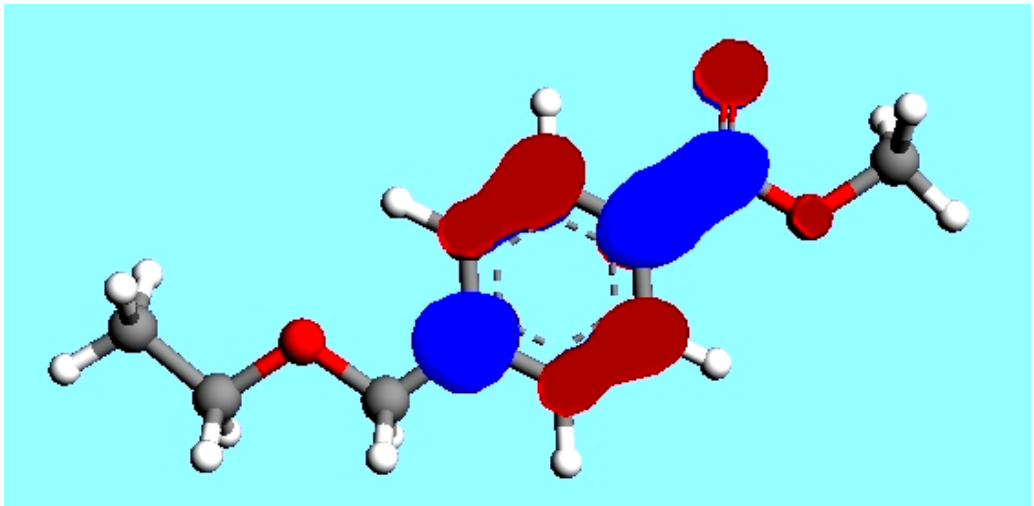


Fig. 5. - LUMO (Lowest Unoccupied Molecular Orbitals) of Methyl-4-(ethoxymethyl)-benzoate as visualised by ArgusLab 4.0.1 , blue shows positive and red shows negative charged MO s.

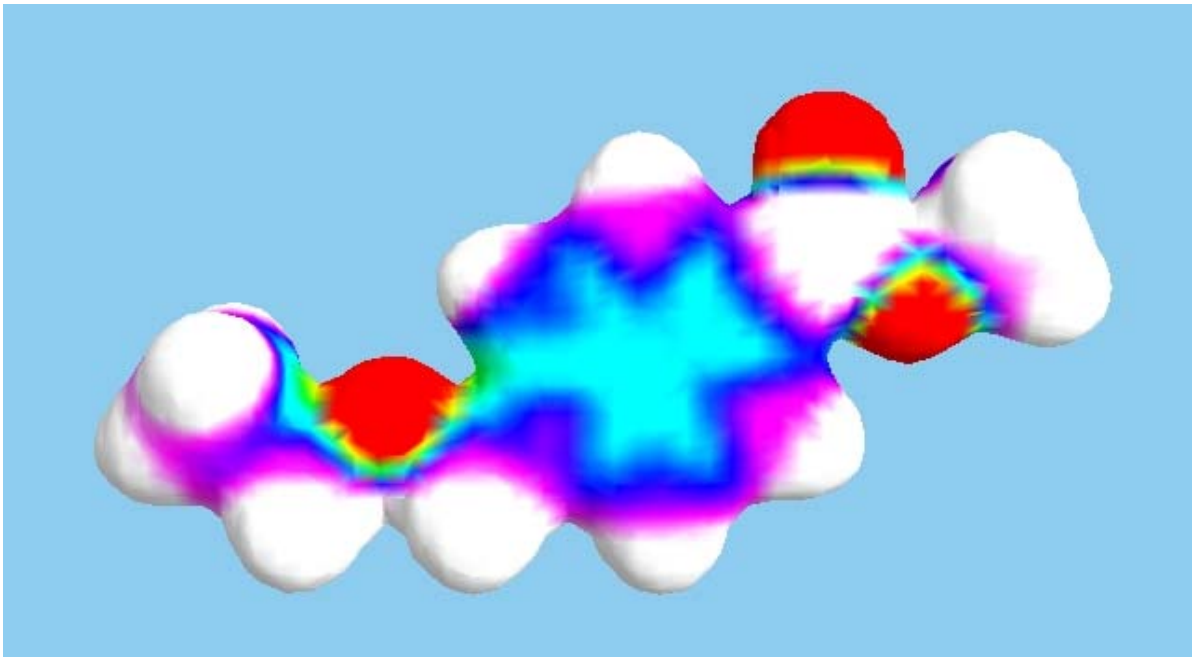


Fig. 6. - The complete surface with the colour map of ESP of Methyl-4-(ethoxymethyl)-benzoate.

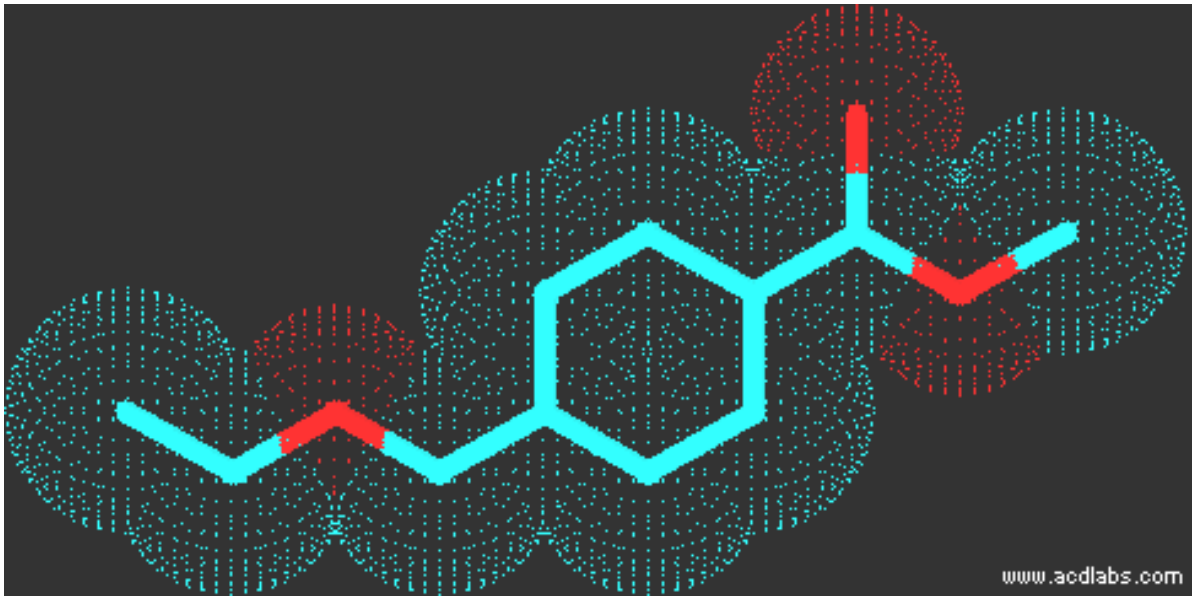


Fig. 7. - 3D view of Methyl-4-(ethoxymethyl)-benzoate visualized by ACD/3D viewer.

Table 1. - List of Mulliken Charges and ZDO charges of Methyl-4-(ethoxymethyl)-benzoate as calculated by ArgusLab suite

Numbering of atoms as shown in the figure	Atoms	Mulliken Charges	ZDO charges
1	C	-0.1321	-0.0726
2	C	-0.1333	-0.1149
3	C	-0.1255	-0.0688
4	C	-0.1794	-0.1206
5	C	-0.0653	-0.0433
6	C	-0.2111	-0.1524
7	H	0.2267	0.1572
8	H	0.2224	0.1538
9	H	0.2305	0.1603
10	H	0.1991	0.1356
11	C	0.3972	0.3442
12	O	-0.3284	-0.2810
13	C	-0.1905	-0.0601
14	O	-0.3863	-0.3552
15	C	-0.0653	0.0125
16	O	-0.3171	-0.2824
17	C	-0.1034	-0.0184
18	C	-0.3532	-0.2157
19	H	0.1384	0.0894
20	H	0.1373	0.0884
21	H	0.1271	0.0813
22	H	0.1144	0.0661
23	H	0.1142	0.0660
24	H	0.1311	0.0807
25	H	0.1312	0.0806
26	H	0.1503	0.0992
27	H	0.1343	0.0840
28	H	0.1371	0.0863

Table 2. - Ground State Dipole (Debye) of Methyl-4-(ethoxymethyl)-benzoate

X	Y	Z	length
-1.23106153	-3.33897775	-0.17334334	3.56291073

Table 3. - List of Bond Angles (in degree) between different atoms of Methyl-4-(ethoxymethyl)-benzoate

C18-C17-O16	106.94^0
C17-O16-C15	111.85^0
O16-C15-C5	109.52^0
C2-C11-O14	125.06^0
C2-C11-O12	114.64^0
O14-C11-O12	117.30^0
C11-O12-C13	116.43^0

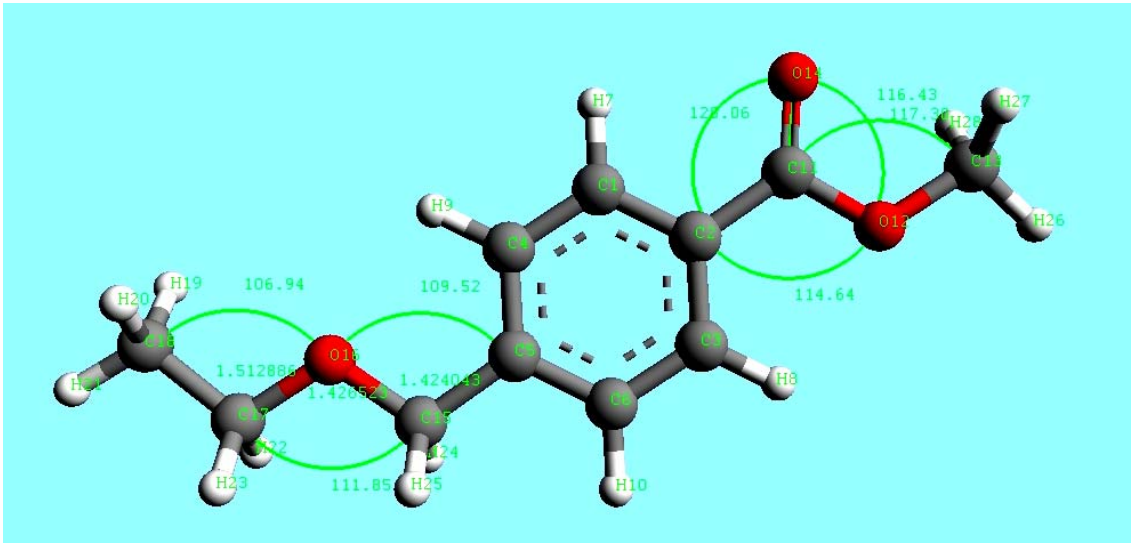


Fig. 8. - Bond angles (in degree) in optimized geometry of Methyl-4-(ethoxymethyl)-benzoate as calculated by ArgusLab suite

Table 4. - Bond distances (in angstrom) in Methyl-4-(ethoxymethyl)-benzoate

C18-C17	1.513
C17-O16	1.426
O16-C15	1.424
C15-C5	1.494
O14-C11	1.233
C11-C2	1.469
C11-O12	1.371
O12-C13	1.426

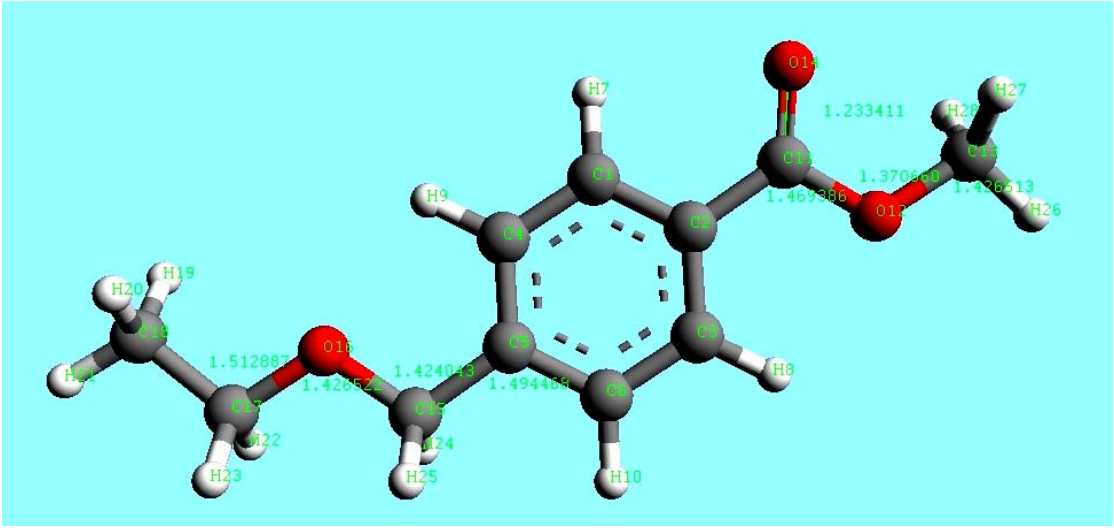


Fig. 9. - Bond distance (in angstrom) in optimized geometry of Methyl-4-(ethoxymethyl)-benzoate as calculated by ArgusLab suite

CONCLUSIONS

The present work indicates the synthesis Methyl-4-(ethoxymethyl)-benzoate under mild, efficient , environment friendly method mediated by $FeSO_4$ without any dry solvents and inert atmosphere and the best conformation of Methyl-4-(ethoxymethyl)-benzoate is found to be **at -110.9143 kcal/mol** which is the heat of formation (minimum potential energy) by using Argus Lab software.

The conformational analysis like bond angles, bond distances, mulliken charges, ZDO charges with minimum potential energy is crucial when establishing SAR/QSAR models using theoretically calculated descriptors, since it can be dependent on the molecular structure.

Finally all geometric variables were completely optimized for the compound and the lowest energy conformation was used in molecular modelling studies.

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