A NEW MICROWAVE ASSISTED SYNTHETIC METHOD FOR THE SYNTHESIS OF 2-(1H-BENZO[D]IMIDAZOL-1-YL)-1-PHENYLETHAN-1-ONE OXIMES: AN EXPERIMENTAL AND COMPUTATIONAL STUDY

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Abstract: This study consists of two parts. In the first part, we have studied on a new microwave assisted synthetic method for the synthesis of 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oximes from corresponding ketones. The results showed that the proposed microwave assisted method is efficient and time and energy saving. In the second part of our study some density functional theory (DFT) calculations have been performed on the selected molecules and compared with the experimental results. In the computational part of the study; single point energy calculations, geometry optimizations, frequency analysis, NMR spectral analysis, molecular electrostatic potential map calculations, frontier molecular orbital calculations, determination of some global reactivity descriptors and Mulliken atomic charge calculations have been performed. All DFT calculations were carried out at the B3LYP/6-31G(d), B3LYP/6-311G(d,p) and B3LYP/6-311+G(2d,p) level of theories.

Keywords: Microwave synthesis, oximes, benzimidazole, DFT calculation, computational chemistry

Introduction

Oximes and related compounds are important compounds in organic chemistry. This type of organic compounds can be very useful for the synthesis of wide range of organic molecules. Additionally, especially with the integration of some certain groups, like imidazole, benzimidazole, triazole, benzotriazole etc. this organic compounds exhibit broad spectrum of biological activities (Jiang, 2011). They can act as antibacterial (Kaplancikli, 2004), antifungal (Madkour, 2006) and antiviral (Beaulieu, 2006) agents etc. Figure 1 represents a typical 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one and its oxime form.

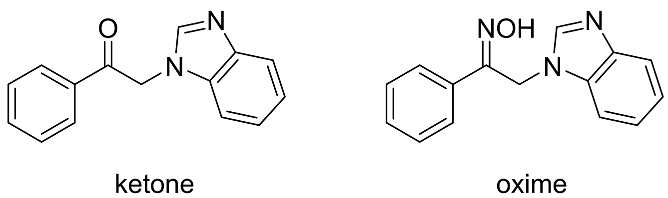


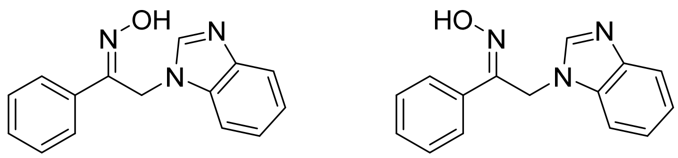
Figure 1. A typical 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one and its oxime form.

Miconazole is an important antifungal agent. It is the active ingredient of some commercially available pharmaceuticals. Oxiconazole is the oxime ether form of miconazole and it is also an important commercially available antifungal agent.

Literature contains various methods for the synthesis of oximes. Oximes can be prepared by the addition of hydroxylamine to aldehydes or ketones (Smith, 2007). This reaction is generally carried out in the presence of bases, and ethyl alcohol is commonly used as solvent. But some other methods also can be used, for example, refluxing in pyridine without using additional base (Abdel-Megid, 2002). Phase transfer reactions also can be used in this type of conversion and PEG-600 and high carbon number phenols, for example, nonyl phenol or dodecylphenol, can increase reaction rate as phase transfer catalysts (Liu, 1997; Krbechek, 1994). Microwave energy can also be used in the transformation of ketones to the corresponding oximes (Puciova, 1992; Mitra, 1999; Hajipour, 1999).

Oxime can be obtained either (E)- or (Z)- isomers. It is related to the relative stability of the isomers which will be the major product. In some cases (E)- isomer is more stable and becomes the major product but in some cases the (Z)- isomer is the major one. Figure 2 represents (E)- and (Z)- forms of 2-(1H-benzo[d]imidazol-1-yl)-1-

phenylethan-1-one oxime.



(Z)-oxime (E)-oxime

Figure 2. (E)- and (Z)- forms of 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime.

One of the methods for the synthesis of 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime is reported by Abdel-Megid (2002). In this method ketone was refluxed in pyridine for 6 hours in the presence of hydroxylamine. The yield was reported as 55%. Another method is reported by Özel Güven (2007). In this method, the reaction was carried out at room temperature in 24 hours. Methanol and water were used as solvents. The reported yield is 65%.

Materials and Methods

This study consists of two parts. In the first part, we have studied on a new microwave assisted synthetic method for the synthesis of 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime from corresponding ketone. However the literature contains various methods for the conversion of this type of ketones to their oxime forms (Abdel-Megid, 2002, Ozel Guven, 2007, Rad, 2009, Roeintan, 2015), the results showed that the proposed microwave assisted method is efficient and time and energy saving. Microwave assisted ketone to oxime conversion reactions was carried out in pyridine in the presence of hydroxylamine hydrogenchloride under 200 W of microwave energy in 30 minutes. Prior to ketone to oxime conversion reaction we have used a two step literature method for the synthesis of ketone (Özel Güven, 2007).

In the second part of our study some density functional theory (DFT) calculations have been performed on the synthesized molecules and compared with the experimental results. In the study; single point energy calculations, geometry optimizations, frequency analysis, NMR spectral analysis, molecular electrostatic potential map calculations, frontier molecular orbital calculations, determination of some global reactivity descriptors and Mulliken atomic charge calculations have been performed. All DFT calculations were carried out at the B3LYP/6-31G(d), B3LYP/6-311G(d,p) and B3LYP/6-311+G(2d,p) level of theories using Gaussian 09W Rev.D.01 Program Package (Frisch, 2013). GaussView 5 Program Package (Dennington, 2009) was used for the visualization of the computational results.

Results and Discussion

In the synthesis of oxime from corresponding ketone, optimal ketone to hydroxylamine hydrogenchloride molar ratio was found to be 1:1.5. The reaction yield was found to be nearly 65%. The optimal microwave energy and microwave irradiation time was found to be 200W and 30 minutes, respectively.

In computational studies, firstly, calculations on the relative stability of the (E)- and (Z)- isomers of 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime was carried out. Energies for the (Z)- and (E)- isomers and the energy differences between two isomers are given in Table 1. Results showed that the (Z)-isomer is more stable than the (E)- isomer.

Table 1: Relative stability of the (E)- and (Z)- isomers of 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime.

Isomer	6-311G(d,p) (hartree)	6-311+G(2d,p) (hartree)	6-311G(d,p) (eV)	6-311+G(2d,p) (ev)
Z	-819.05482657	-819.08865299	-22287.62533962	-22288.54580374
E	-819.05307601	-819.08814267	-22287.57770444	-22288.53191722
ΔE	0.00175056	0.00051032	0.04763518	0.01388652

For a comparison, the same calculation was carried out on the imidazole substituted oxime. Results for the calculations on the relative stability of the (E)- and (Z)- isomers of 2-(1H-imidazol-1-yl)-1-phenylethan-1-one oxime are given in Table 2. It can be seen that the energy differences between (E)- and (Z)- isomers for the imidazole substituted oxime is bigger than the benzimidazole substituted oxime. The (Z)- isomer is again the more stable isomer.

Table 2: Relative stability of the (E)- and (Z)- isomers of 2-(1H-imidazol-1-yl)-1-phenylethan-1-one oxime.

Isomer	6-311G(d,p) (hartree)	6-311+G(2d,p) (hartree)	6-311G(d,p) (eV)	6-311+G(2d,p) (ev)
Z	-665.37104241	-665.39952978	-18105.67500978	-18106.45019089
E	-665.36881286	-665.39858609	-18105.61434061	-18106.42451177
ΔE	0.00000941	0.00094369	0.06066917	0.02567912

Calculated and experimentally obtained selected geometric parameters for the 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime was given in Figure 3 and Table 3. Calculated values were obtained at the B3LYP/6-311+G(2d,p) level of theory. Experimental geometric parameters are literature values (Özel Güven, 2007). The results show that there is a good agreement between the experimental and computational results.

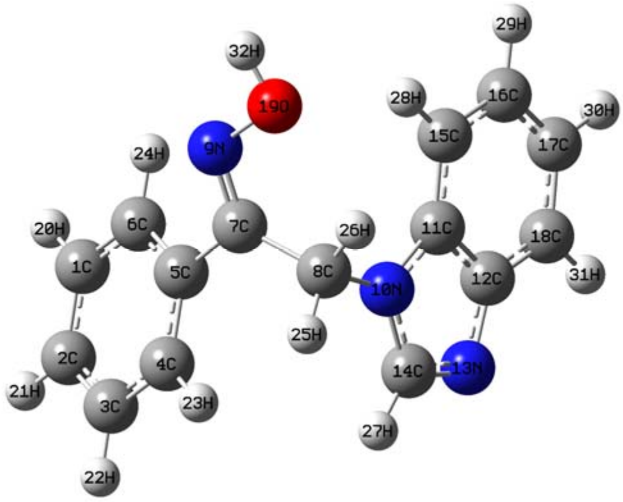


Figure 3. Calculated molecular structure for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime at the B3LYP/6-311+G(2d,p) level of theory.

Table 3: Calculated and experimental geometric parameters for the 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime.

Bond Angle	Calculated	Literature	Bond Length	Calculated	Literature
6C-5C-7C	120.2	120.2	**19O-32H**	0.964	0.870
5C-7C-9N	116.0	115.3	**9N-19O**	1.407	1.383
7C-9N-19O	113.7	111.4	**9N-7C**	1.279	1.300
9N-19O-32H	102.2	107.0	**7C-5C**	1.484	1.491
9N-7C-8C	124.0	124.0	**7C-8C**	1.521	1.478
7C-8C-10N	112.9	111.5	**8C-10N**	1.454	1.479
7C-8C-10N	127.1	127.5			

Molecular electrostatic potential maps for the 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one and 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime were given in Figure 4 and Figure 5, respectively.

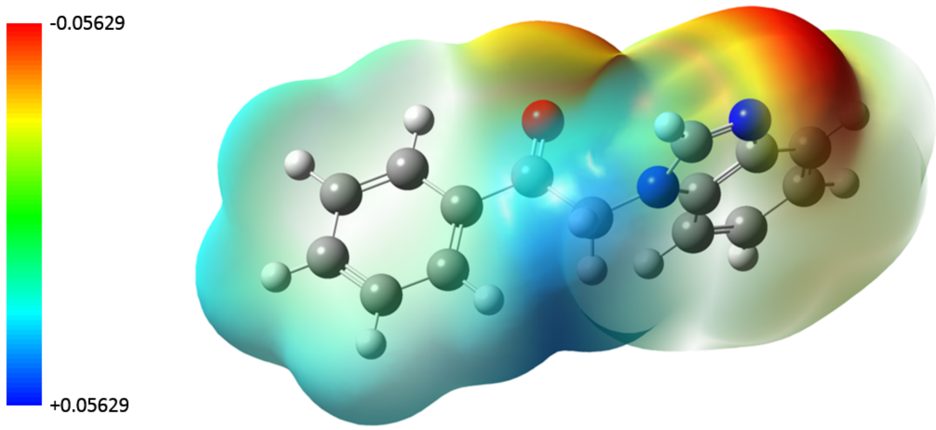


Figure 4. Molecular electrostratic potential map for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one.

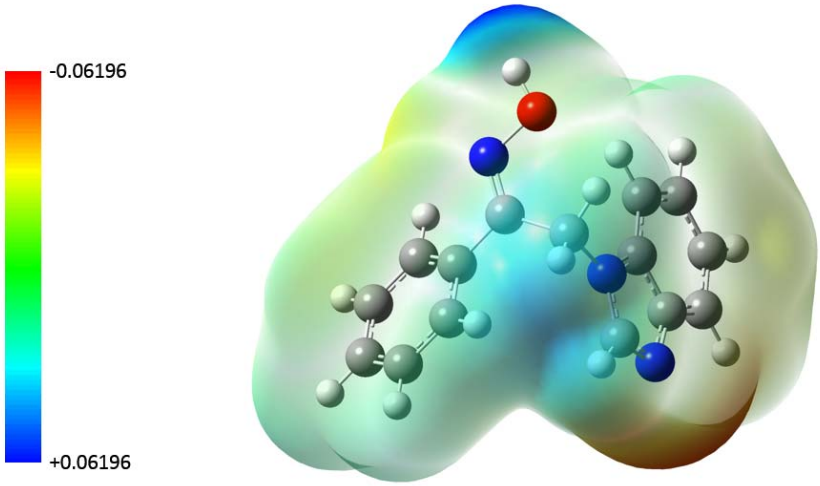
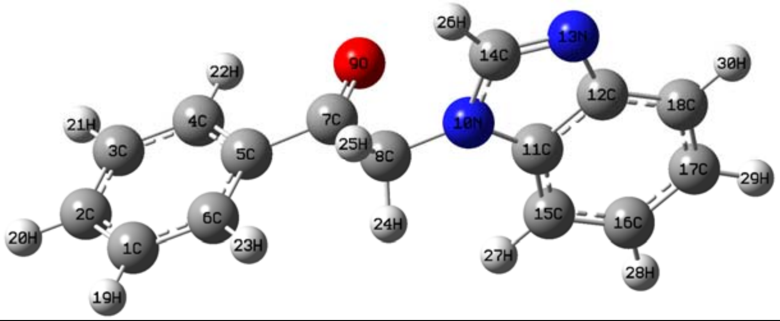


Figure 5. Molecular electrostatic potential map for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime.

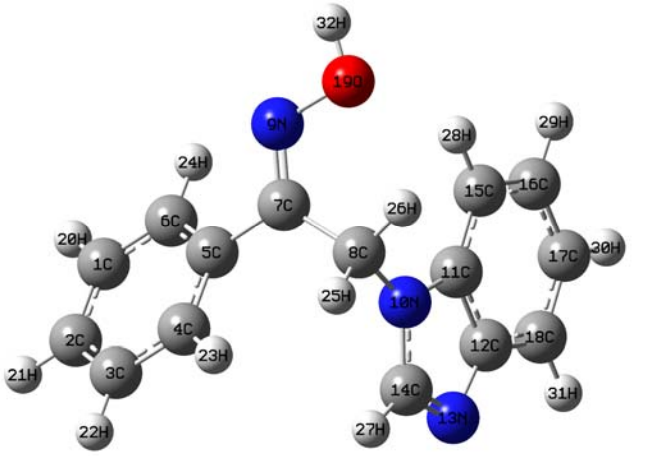
In computational studies, NMR shielding tensor prediction calculations also have been performed. Calculated ^{1}H NMR chemical shifts at the B3LYP/6-31G(d), 6-311G(d,p) and 6-311+G(2d,p) level of theories using both CSGT and GIAO methods and for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one were given in Table 4 and for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime were given in Table 5. Table 4 and Table 5 also includes experimental ^{1}H NMR chemical shifts obtained from the literature (Wen-lin, 2013; Abdel-Megid, 2002). In Table 4 and Table 5, Exp. denotes experimental values obtained from literature, csgt1 denotes B3LYP/6-31G(d) CSGT, csgt2 denotes B3LYP/6-311G(d,p) CSGT, csgt3 denotes B3LYP/6-311+G(2d,p) CSGT, giao1 denotes B3LYP/6-31G(d) GIAO, giao2 denotes B3LYP/6-311G(d,p) GIAO, giao3 denotes B3LYP/6-311+G(2d,p) GIAO.

Table 4: [1]H NMR Chemical Shifts for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one.



	Exp.	csgt1	csgt2	csgt3	giao1	giao2	giao3
22-H	7.94-7.97	4.77	6.82	8.10	7.70	8.51	8.74
23-H	7.94-7.97	4.77	6.82	8.10	7.70	8.51	8.74
30-H	7.79-7.83	4.73	6.83	7.82	7.36	8.25	8.33
20-H	7.56-7.61	4.65	6.57	7.58	7.23	7.98	8.17
19-H	7.43-7.48	4.59	6.52	7.47	7.18	7.90	8.06
21-H	7.43-7.48	4.59	6.52	7.47	7.18	7.90	8.06
26-H	8.15	3.80	6.45	7.40	6.85	7.74	8.05
29-H	7.32-7.37	4.31	6.18	7.16	6.90	7.65	7.75
28-H	7.25-7.28	4.25	6.12	7.08	6.84	7.58	7.68
27-H	7.25-7.28	3.96	6.01	6.94	6.55	7.33	7.47
24-H	6.08	2.61	4.12	5.34	4.73	5.49	5.85
25-H	6.08	2.61	4.12	5.34	4.73	5.49	5.85

Table 5: [1]H NMR Chemical Shifts for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime.



	Exp.	csgt1	csgt2	csgt3	giao1	giao2	giao3
28-H	6.8-7.6	4.60	6.78	7.61	7.16	7.87	7.99
31-H	6.8-7.6	4.57	6.68	7.60	7.15	7.84	7.88
23-H	6.8-7.6	4.29	6.48	7.47	6.91	7.73	7.77
24-H	6.8-7.6	4.29	6.48	7.47	6.91	7.73	7.77
27-H	6.8-7.6	3.59	6.41	7.38	6.65	7.59	7.73
21-H	6.8-7.6	4.47	6.31	7.24	6.92	7.46	7.55
20-H	6.8-7.6	4.46	6.33	7.22	6.91	7.46	7.53
22-H	6.8-7.6	4.46	6.33	7.22	6.91	7.46	7.53
29-H	6.8-7.6	4.32	6.15	7.11	6.86	7.38	7.47
30-H	6.8-7.6	4.29	6.14	7.08	6.85	7.36	7.43
32-H	11.0	2.74	5.91	6.98	6.09	6.96	7.15
25-H	5.6	2.55	4.16	5.27	4.75	5.42	5.60
26-H	5.6	2.55	4.16	5.27	4.75	5.42	5.60

Results show that calculated [1]H NMR chemical shifts at the B3LYP/6-311G(d,p) GIAO (giao2) and especially B3LYP/6-311+G(2d,p) CSGT (csgt3) level of theories show good agreement with the experimental results.

Figure 6 represents the vibrational spectra calculated at the B3LYP/6-311+G(2d,p) level of theory for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one and 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime.

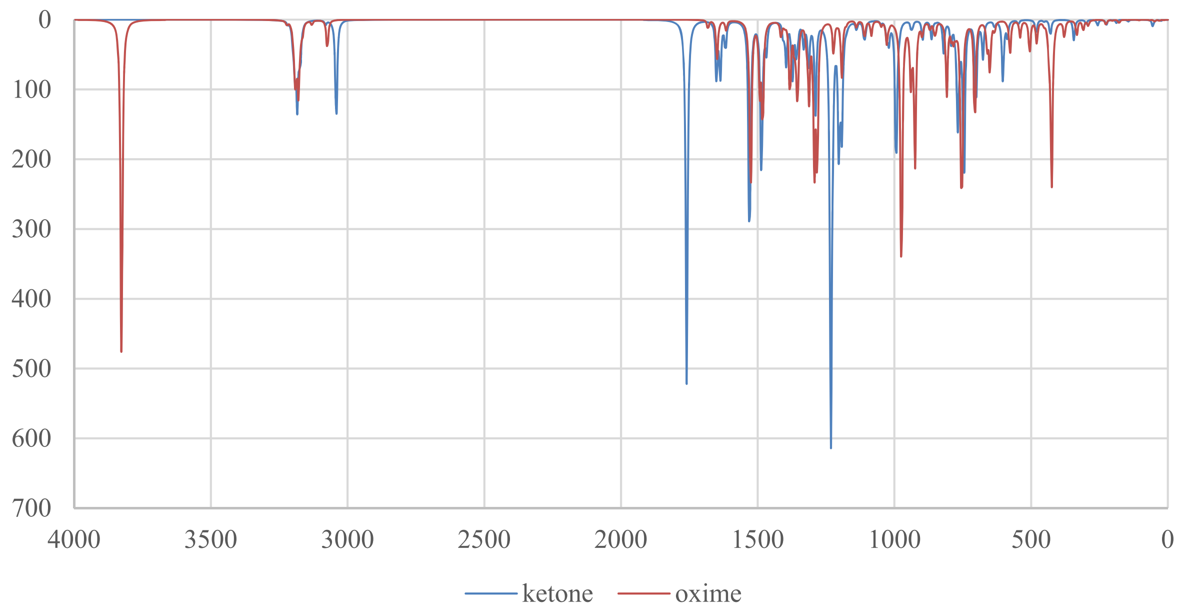


Figure 6. Calculated vibrational spectra for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one and 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime at the B3LYP/6-311+G(2d,p) level of theory.

Figure 7 represent HOMO and LUMOs of 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one and 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime calculated at the B3LYP/6-311+G(2d,p) level of theory.

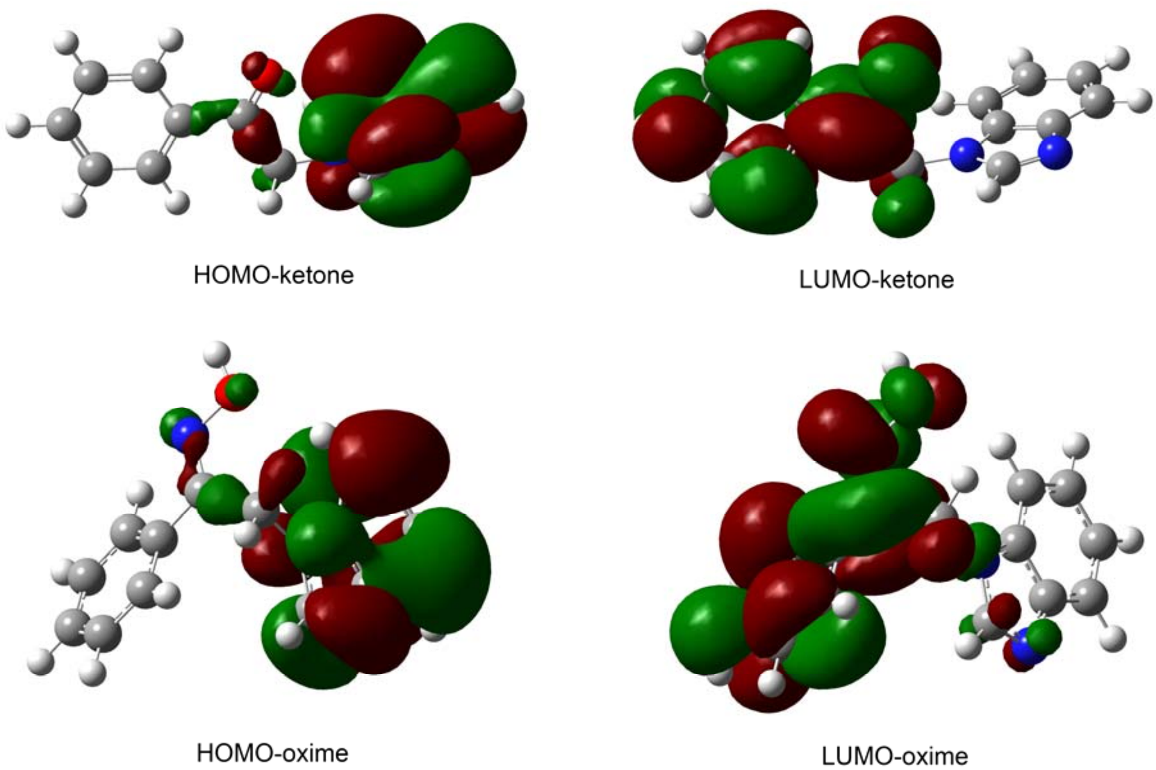


Figure 7.Highest Occupied and Lowest Unoccupied Molecular Orbitals for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one and 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime.

Table 6: Calculated global reactivity descriptors for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one and 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime at the 6-311+G(2d,p) level of theory.

	ketone		oxime	
	6-311+G(2d,p)	6-311+G(2d,p)	6-311+G(2d,p)	6-311+G(2d,p)
LUMO	-0.08601	-2.32227	-0.05937	-1.60299
HOMO	-0.22951	-6.19677	-0.22959	-6.19893
HOMO-LUMO Gap	0.14350	3.87450	0.17022	4.59594
I	0.22951	6.19677	0.22959	6.19893
A	0.08601	2.32227	0.05937	1.60299
χ	0.15776	4.25952	0.14448	3.90096
η	0.07175	1.93725	0.08511	2.29797
S	6.96864	0.25810	5.874750323	0.217583345
μ	-0.15776	-4.25952	-0.14448	-3.90096
ω	0.17344	4.68280	0.122632302	3.311072147

Figure 8 represents Mulliken atomic charges for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one and Figure 9 represents for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime.

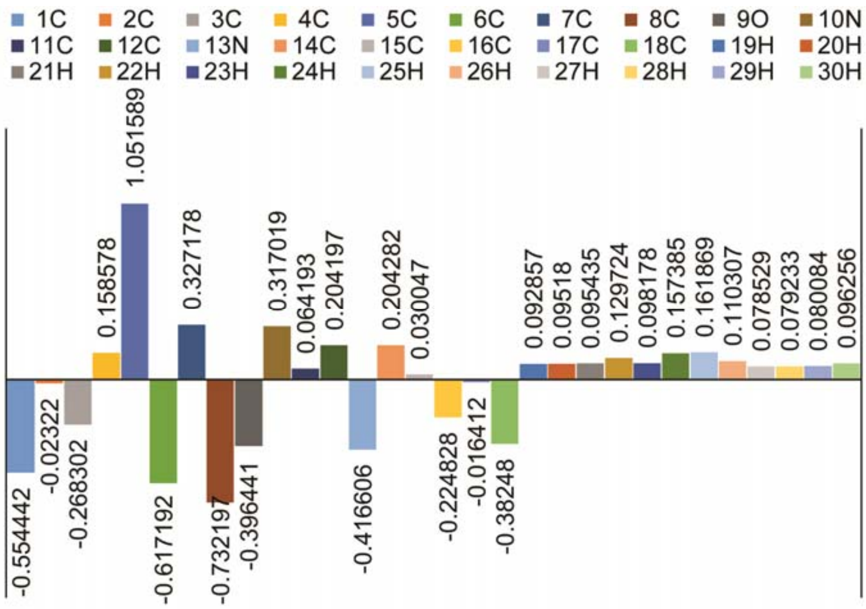


Figure 8. Mulliken atomic charges for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one calculated at the B3LYP/6-311+G(2d,p) level of theory.

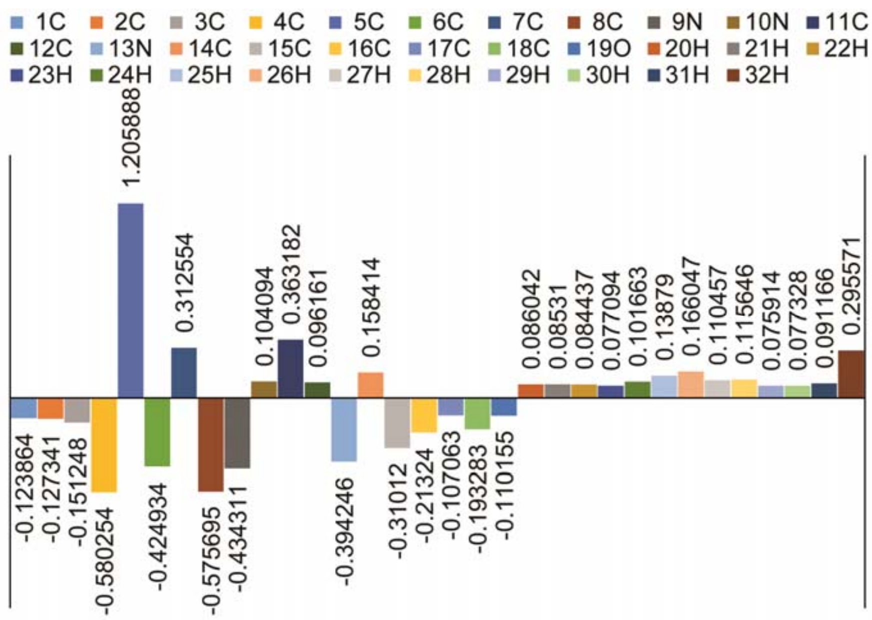


Figure 9. Mulliken atomic charges for 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime calculated at the B3LYP/6-311+G(2d,p) level of theory.

Conclusion

As a result, in this study we have been studied on 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one oxime. The study consist of two parts. In the first part we have been studied on a new microwave assisted synthetic method for the conversion of 2-(1H-benzo[d]imidazol-1-yl)-1-phenylethan-1-one to its oxime form. The results showed that the proposed microwave assisted method is efficient and time and energy saving. In the second part of our study we have performed some density functional theory calculations on the selected molecules and compared them with the experimental results obtained from the literature. In the synthesis of oxime from corresponding ketone, the major product is the (Z)- isomer. This is not a surprising result because of the more stable structure of the (Z)- isomer than the (E)- isomer. Computational results also support this experimental results. There is a considerable energy difference between the (E)- and (Z)- isomers and the (Z)- isomer is the more stable one. In ^{1}H NMR chemical shift calculations there is a good agreement between the calculated values and the experimental values obtained from the literature. The best results have been obtained from the calculations performed at the B3LYP/6-311+G(2d,p) CSGT and B3LYP/6-311G(d,p) GIAO.

Acknowledgements

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