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Microwave assisted one pot synthesis, Mass spectral analysis and DFT studies of 6-Substituted-3,4-dihydro-4-phenylpyrimidin-2(1H)-one

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Abstract-

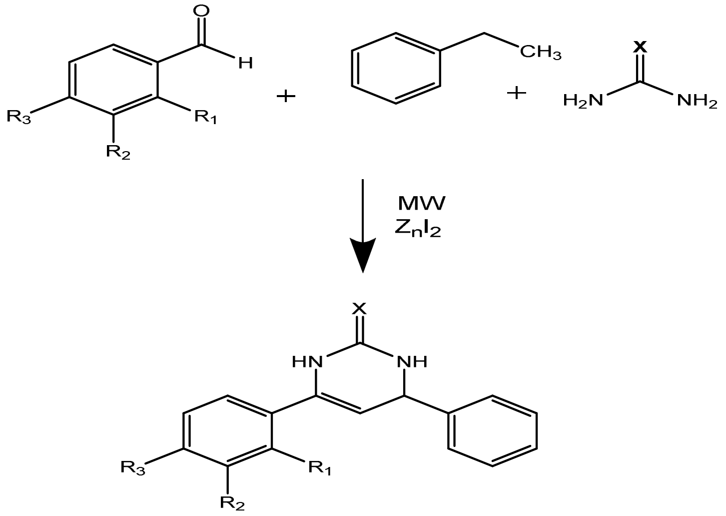
One pot synthesis of 6-substituted-3,4-dihydro-4-phenylpyrimidin-2(1H)-ones was carried out by the condensation of substituted benzaldehyde, acetophenone and urea/thiourea with a catalytic amount of ZnI_2 under microwave irradiation. The compounds synthesized were characterized by their mass and NMR spectral data. The structural and electronic properties of these compounds have been investigated theoretically by performing semi-empirical molecular orbital theory at the level of PM6 of theory and Density Functional theory at the B3LYP/6-31G(d) levels of theory. The optimized structures, relative binding energies, position of HOMO and LUMO of the molecules are obtained. In this paper the synthesis, mass spectral analysis and DFT studies of 12 compounds of this series are being reported.

Keywords: Biginelli, Microwave, HOMO, LUMO, DFT

Introduction

Biginelli reaction is a simple one pot condensation of an aldehyde, ketoester, urea in a solvent such as ethanol using a strongly acidic catalyst, that is, hydrochloric acid to produce 3,4-dihydropyrimidin-2-(1H)-ones [1]. However**,** the yields of products were very low. From then on, many new techniques, such as microwave assisted synthetic techniques, ionic liquids ultrasound irradiation, solvent-free techniques and many new catalysts, such as $InBr_3$, $ZrCl_4$, $BiCl_3$ etc, were used to improve this transformation. In spite of their potential utility, many of these methods involve expensive reagents, strongly acidic conditions, long reaction time, high temperature and stoichiometric amounts of catalysts and unsatisfactory yields. The first Biginelli like reaction was conducted in CH_3CN by using aldehydes, ketones, and urea as substrates and $FeCl_3.6H_2O$ and TMSCl as catalysts, which remarkably broadened the Biginelli reaction [2]. However, suffered from its drawbacks, especially the use of highly toxic organic solvent, long reaction time (12h) and stoichiometric TMSCl, many catalysts or promoters, such as CH_3COOH, $Fe_2(SO_4)_3$, $MgSO_4$, HCl, H_2SO_4, etc, were used to explore the reaction under solvent-free microwave assisted conditions [3]. These results suggest that most of the Lewis acids and Bronsted acids could promote the reaction, but the yields are not so high. In comparison with other catalysts, the use of 1.5 mmol of ZnI_2 could make the yield reach 48% under microwave irradiation [4]. The reason for ZnI_2 being the best catalyst may be its strongly acidic character[4]. In order to examine the substrate scope of this Biginelli-like reaction, various aromatic aldehydes with different substituent using ZnI_2 were used under the optimized reaction condition to synthesize a series of 5**-**unsubstituted-3,4-dihydropyrimidin-2(1H)-ones [5]**.** Apart from synthesis, the effect of molecular structure on the chemical reactivity has been a subject of great interest in several disciplines of chemistry [6]. The quantum chemical calculations have been widely used to study the chemical reactivity as well as to solve chemical ambiguities. The geometry of the molecules in the ground and excited state, as well as the nature of their molecular orbitals, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are involved in the properties of activity of compounds.

The objective was to synthesize 3,4-dihydropyrimidin-2-(1H)-ones by a single step condensation reaction (**scheme 1**) and to investigate the reactivity of these compounds on theoretical chemical parameters such as the energies of highest occupied molecular orbital (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}), the energy difference (ΔE) between E_{HOMO} and E_{LUMO}, dipole moment (μ) and total energy (TE).



X= O (compound no. 1-7)
X= S (compound no. 8-12)

Scheme 1

No.	Name	$-R_1$	$-R_2$	$-R_3$
1	3,4-dihydro-6-(2-hydroxyphenyl)-4-phenylpyrimidin-2(1H)-one	-OH	-H	-H
2	6-(4-(dimethylamino)phenyl)-3,4-dihydro-4-phenylpyrimidin-2(1H)-one	-H	-H	$-N(CH_3)_2$
3	3,4-dihydro-6-(3-hydroxyphenyl)-4-phenylpyrimidin-2(1H)-one	-H	-OH	-H
4	3,4-dihydro-6-(2,4-dihydroxyphenyl)-4-phenylpyrimidin-2(1H)-one	-OH	-H	-OH
5	6-(3-ethoxy-2-hydroxyphenyl)-3,4-dihydro-4-phenylpyrimidin-2(1H)-one	-OH	$-OC_2H_5$	-H
6	3,4-dihydro-6-(4-nitrophenyl)-4-phenylpyrimidin-2(1H)-one	-H	-H	$-NO_2$
7	6-(2,3-diethoxyphenyl)-3,4dihydro-4-phenylpyrimidin-2(1H)-one	-H	$-OC_2H_5$	$-OC_2H_5$
8	3,4-dihydro-6-(2-hydroxyphenyl)-4-phenylpyrimidin-2(1H)-thione	-OH	-H	-H
9	6-(4-(dimethylamino)phenyl)-3,4-dihydro-4-phenylpyrimidin-2(1H)-thione	-H	-H	$-N(CH_3)_2$
10	3,4-dihydro-6-(2,4-dihydroxyphenyl)-4-phenylpyrimidin-2(1H)-thione	-OH	-H	-OH
11	3,4-dihydro-6-(4-nitrophenyl)-4-phenylpyrimidin-2(1H)-thione	-OH	-H	$-OC_2H_5$
12	6-(2,3-diethoxyphenyl)-3,4-dihydro-4-phenylpyrimidin-2(1H)-thione	-H	$-OC_2H_5$	$-OC_2H_5$

Experimental

All reactions were performed on a domestic microwave oven (Power 1200 W). All reactants were obtained from commercial sources and freshly distilled prior to use. Melting points were taken in an electrically heated instrument and are uncorrected. Compounds were routinely checked for their purity on silica gel TLC plates and the spots were visualized by iodine vapors. IR spectra were recorded on Shimadzu 8201 PC FTIR spectrometer. PMR spectra were recorded on Bruker DRX 300 MHz FT NMR spectrometer using TMS as internal reference and chemical shift values are expressed in δ units. Mass spectra were run on Jeol SX – 102 spectrometer.

General Procedure

For the synthesis of compounds 1-12, a mixture of the appropriate aldehyde, acetophenone and urea or thiourea in equimolar concentration with a catalytic amount of ZnI_2 in a 100ml glass tube was irradiated in a microwave oven in bursts of 15-20 seconds. The reaction was monitored by TLC. After the reaction was completed, distilled water was added into the flask and stirred for several minutes and then filtrated through a sintered funnel to afford crude product, which was further purified by recrystallization (EtOH). Reaction details are given in **Table 1**.

Table 1: Reaction Details

No.	Aldehyde	Amide	Time (Minutes)	Yield (%)	Mp (°C)
1	2-hydroxybenzaldehyde	Urea	6	65.5	250
2	4-dimethylaminobenzaldehyde	Urea	5	63.0	240
3	3-hydroxybenzaldehyde	Urea	6	75.2	232
4	2,4-dihydroxybenzaldehyde	Urea	6	55.0	265
5	3-ethoxy,2-hydroxybenzaldehyde	Urea	7	68.3	215
6	4-nitrobenzaldehyde	Urea	8	66.1	227
7	3,4-diethoxybenzaldehyde	Urea	5	70.0	260
8	2-hydroxybenzaldehyde	Thiourea	6	74.8	255
9	4-dimethylaminobenzaldehyde	Thiourea	6	65.0	242
10	2,4-dihydroxybenzaldehyde	Thiourea	5	67.0	234
11	3-ethoxy,2-hydroxybenzaldehyde	Thiourea	6	78.0	230
12	2,3-diethoxybenzaldehyde	Thiourea	5	76.0	222

Table 2: Spectral Data

No.	Mass (m/z)	^{1}H NMR Data (DMSOd_6)
1	266,250,190,174,150,98	7.06-7.14(m, 5H, ArH), 6.61-7.04(m, 4H, ArH), 6.0(S, 1H, NH), 5.94(s, 1H, CH).
2	293,250,217,174,98	7.06-7.14(m, 5H, ArH), 6.61-7.04(m, 4H, ArH), 6.0(s, 1H, NH), 5.94(s, 1H, CH), 4.87(s, 1H, CH), 2.85(s, 3H, CH_3).
3	266,250,198,174,98	7.06-7.14(m, 5H, ArH), 6.61-7.04(m, 4H, ArH), 6.0(s, 1H, NH), 5.94(s, 1H, CH), 4.87(s, 1H, CH).
4	282,266,226,250,206,174,98	7.06-7.14(m, 5H, ArH), 6.15-6.96 (m, 3H, ArH), 6.5(s, 1H, CH), 5.0(s, H, ArOH), 6.0(s, 1H, NH), 4.59(s,1H, CH).
5	310,294,266,250,234,174,98	7.06-7.14(m, 5H, ArH), 6.48-6.69 (m, 3H, ArH), 6.0(s, 1H, NH), 5.56(s, 1H, CH), 5.0 (s, H, ArOH), 3.98(q, 2H, CH_2), 1.33(t, 3H, CH_3).
6	295,250,219,174,98	7.56-8.14(m, 4H, ArH), 7.06-7.14 (m, 5H, ArH), 6.23(s, 1H, CH) 6.0(s, 1H, NH**).**
7	338,294,233,261174,98	7.06-7.14(m, 5H, ArH), 6.61-6.75 (m, 3H, ArH), 6.0(s, 1H, NH), 5.56(s, 1H, CH), 3.98(q, 2H, CH_2), 1.33(t, 3H, CH_3).
8	282,266,206,190,114	7.06-7.14(m, 5H, ArH), 6.77-7.13 (m, 4H, ArH), 6.5(s, 1H, CH), 5.0(s, 1H, ArOH), 2.0(s, 1H, NH).
9	309,265,233,190,114	7.06-7.14(m, 5H, ArH), 6.54-7.12(m, 4H, ArH), 4.59(s, 1H, CH), 2.85(s, 3H, CH_3), 2.0(s, 1H, NH).
10	298,282,266,222,206,114	7.06-7.14(m, 5H, ArH), 6.24-6.96 (m, 3H, ArH), 6.5 (d, 1H, CH), 5.0(s, 1H, ArOH), 4.59(d, 1H, CH), 2.0(s, 1H, NH).
11	326,310,282,250,190,114	7.06-7.14(m, 5H, ArH) ,6.48-6.69 (m, 3H, ArH), 6.5(d,1H, CH), 5.0(s, 1H, ArOH), 3.98(q, 2H, CH_2), 2.0(s,1H, NH), 1.33(t, 3H, CH_3),
12	352,325,310,282,278,190,114	7.06-7.14(m, 5H, ArH), 6.61-6.75 (m, 3H, ArH), 6.5 (d,1 H, =CH), 5.56(s, 1H, CH), 4.59(d,1H, CH), 3.98(q, 2H, CH_2), 2.0(s,1H, NH), 1.33(t, 3H, CH_3),

Computational Method

Computational studies have led to models to understand some classic and contemporary asymmetric reactions involving inexpensive inorganic catalysts. Complete geometrical optimization of the investigated molecules are performed using PM6 semi-empirical molecular orbital (MO) method and Density Functional Theory (DFT) with the Beck's three parameter exchange functional along with the Lee-Yang-Parr nonlocal correlation functional (B3LYP) [7-9] with 6-31G(d) basis set which is implemented using Gaussian09 package [10]. This approach is shown to yield favorable geometries for a wide variety of systems. This basis set gives good geometry optimization. The geometry was optimized under no constraint. The structure of compound 1 is shown in **Figure1.** All the molecules were subjected to geometry optimization in ground state. The following quantum chemical parameters were calculated from the obtained optimized structure: The highest occupied molecular orbital (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}), the energy difference (ΔE) between E_{HOMO} and

E_{LUMO}, dipole moment (μ) and total energy (TE). The total energy, energy of HOMO and LUMO, ΔE (in a.u.) and the dipole moment, μ (in Debyes) for the molecules 1 to 12, studied by semi-empirical MO method and DFT method are reported in **Table. 3.**

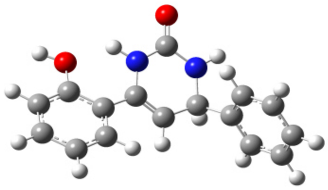


Figure 1: Optimized Molecular Structure of compound 1

Table 3: The Total energy; MO energy of the lowest (HOMO) and highest (LUMO) levels; ΔE (in a.u.) and the dipole moment (μ, in Debyes) for the studied molecules

Compound No.	Method	Total energy	HOMO	LUMO	ΔE (a.u.)	μ (D)
1	SE-PM6 DFT	-0.04224 -878.09219	-0.32504 -0.20093	-0.02139 -0.03189	0.30365 0.16904	5.1263 4.3046
2	SE-PM6 DFT	0.02559 -936.84555	-0.30875 -0.18539	-0.00317 -0.01851	0.30558 0.16688	6.7752 5.7433
3	SE-PM6 DFT	-0.04355 -878.09342	-0.33566 -0.20953	-0.01833 -0.03438	0.31733 0.17515	3.7618 3.7711
4	SE-PM6 DFT	-0.11728 -953.30815	-0.32311 -0.19637	-0.02034 -0.02403	0.30277 0.17234	4.7404 4.3061
5	SE-PM6 DFT	-0.11437 -1031.93463	-0.32295 -0.19676	-0.02153 -0.02731	0.30142 0.16945	6.3492 5.9174
6	SE-PM6 DFT	0.02195 -1007.37751	-0.34814 -0.22069	-0.06506 -0.09827	0.28308 0.12242	4.9033 4.7879
7	SE-PM6 DFT	-0.11809 -1110.55194	-0.31522 -0.19948	-0.00980 -0.02367	0.30542 0.17581	6.2865 4.7305
8	SE-PM6 DFT	0.04287 -1201.05086	-0.31011 -0.19529	-0.02730 -0.04148	0.28281 0.15381	8.0933 6.0746
9	SE-PM6 DFT	0.11034 -1259.80446	-0.30916 -0.19027	-0.01054 -0.03169	0.29862 0.15858	9.4354 7.3815
10	SE-PM6 DFT	-0.03226 -1276.26710	-0.31002 -0.19355	-0.02564 -0.03441	0.28438 0.15914	7.6271 5.8129
11	SE-PM6 DFT	-0.02848 -1354.89139	-0.31028 -0.19448	-0.02300 -0.03538	0.28728 0.15910	8.6930 8.0507
12	SE-PM6 DFT	-0.03009 -1433.51258	-0.31268 -0.19732	0.01452 -0.03611	0.29816 0.16121	6.9825 5.9757

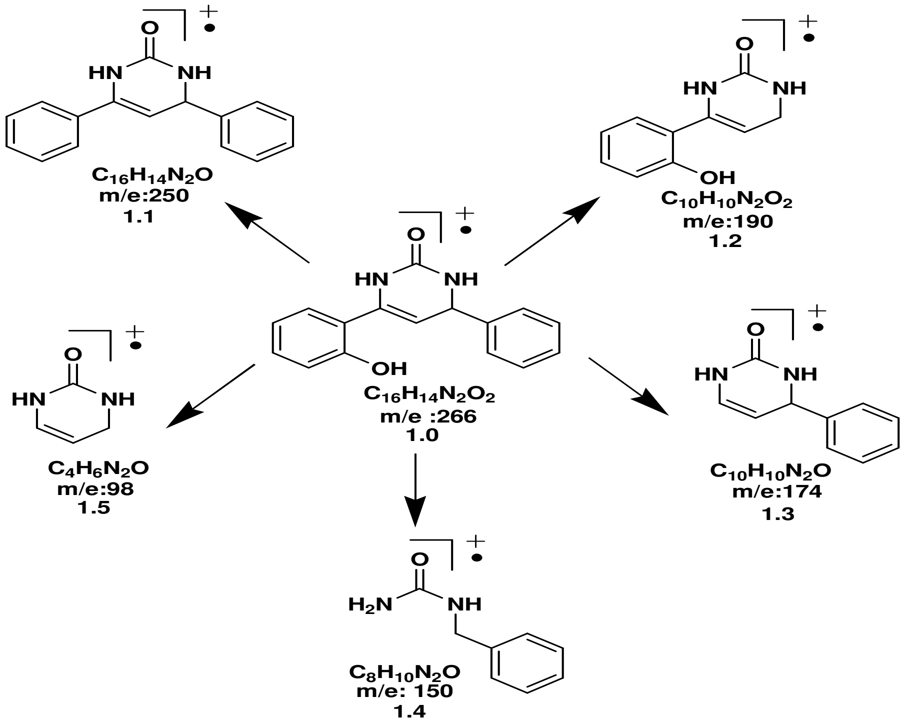
Results and Discussions

Mass Spectral Analysis

Mass spectral studies of 6-Substituted-3,4-dihydro-4- phenylpyrimidin-2(1H)-one has shown variation in fragmentation only due to differently substituted phenyl ring, hydroxyl group, ethoxy group, nitro group, dimethylamino group. All the compounds in general have exhibited a similar pattern of fragmentation. The mass and NMR spectral data of the compounds are given in **Table 2**. The mass fragmentation pattern for 3,4-dihydro-6-(2-hydroxyphenyl)-4-phenylpyrimidin-2(1H)-one (compound 1) is shown in **Scheme 2**.

HOMO-LUMO Analysis

The HOMO-LUMO plot of the heterocycles was obtained by DFT at B3LYP/6-31G(d) level of theory. The lobal region represents the electron distribution in the molecules in HOMO and LUMO. According to frontier molecular orbital theory (FMO) of chemical reactivity, electronic transition is due to interaction between highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of reacting species [11].



Scheme 2

The energy of highest occupied molecular orbital (E_{HOMO}) measures the tendency towards the donation of electron by a molecule. Therefore, higher values of E_{HOMO} indicate better tendency towards donation of electron. Lower the value of LUMO, higher the probability to accept electrons. So the energy gap (ΔE) between HOMO and LUMO is an important stability index. A low gap value refers to the higher electronic transition and vice-versa. The HOMO-LUMO plot of compound 1 is shown in Figure 2.

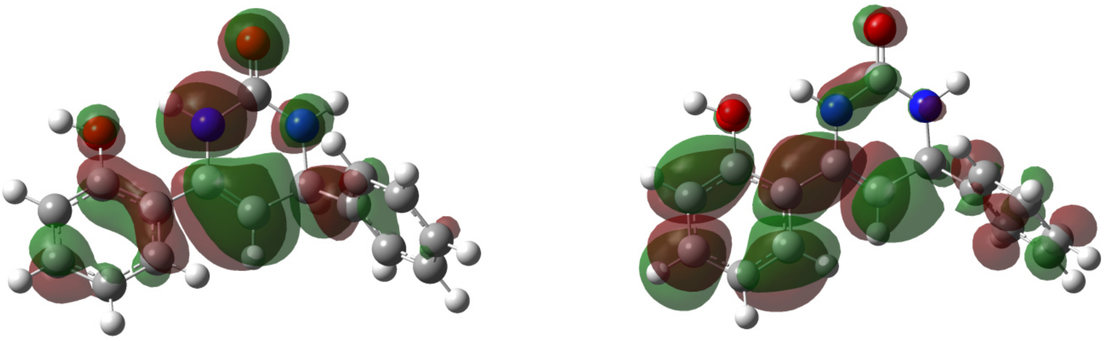

HOMO **LUMO**

Figure 2: HOMO- LUMO plots of Heterocycle 1 (through DFT)

It reveals that in the ground state a little electron density is spread on the substituted benzene ring and more on the pyrimidine ring containing oxygen, whereas in excited state the electron distribution pattern is reversed with addition of a little distribution of electron density over unsubstituted benzene ring. This means that the compound 1 is more active in excited state than in ground state. The compound no. 2-5; 7-12 are also more active in excited state than in ground state. While in molecule 6 both ground and excited state are equally active. In compounds 1-7, O atom is the main site and in compounds 8-12, S atom is the main site of action in ground state which can undergo electrophilic addition-substitution reaction. And in their respective excited state, the conjugated ring system can undergo electrophilic substitution-addition reaction.

Comparing HOMO-LUMO gap energies for different derivatives, it is possible to verify that these compounds are the derivatives with lower energy gap. Comparison between the two groups of compounds (sulfur and oxygen-containing ones) shows that the sulfur-containing heterocyclic compounds are those having lowest energy gaps, suggesting higher chemical reactivity for the latter. Compound no. 6 was found to be most reactive; this is due to the presence of electron withdrawing group.

Conclusion

In summary, a series of novel compounds 1-12 has been synthesized by single pot condensation of aldehyde, ketoester, urea under solvent free condition using ZnI_2 as catalyst under microwave irradiation. The quantum chemical investigation on the geometries and electronic properties of various compounds is performed using PM6 semi-empirical molecular orbital (MO) method and DFT method. Since the molecules are polar and active, in solution phase they may interact strongly with their environment. It also gives useful information regarding the reactivity of the synthesized compounds and leads us to the conclusion that sulfur-containing heterocyclic compounds are more reactive than the homologous oxygen-containing compounds. Good information about the active sites in the molecules is obtained which clarify the nucleophilic or electrophilic substitution sites in the molecules.

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