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Synthesis and Chemical Reaction of 2-Oxazoline 5-Ones Derivatives

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Abstract

Owing the wide use of oxazoline compounds as starting materials for the preparation of heterocycles and their uses are still explored and some of wide application for industrial and biological fields, 2-oxazoline nucleus has formed a large number of potentially biologically active molecules on modifications. The synthesis, structures and biological activities of oxazoline derivatives have long been focused of research interest of organic chemists in the field of medicine, due to the potential biological activities exhibited by them. Looking into the medicinal importance of oxazoline moiety, it will be worthwhile to synthesize certain newer derivatives of oxazolines and evaluate them for their biological activities, in this research work we synthesize some new derivatives of oxazoline. Compound 4-benzyliden -2-(4-nitro- phenyl) 4H-oxazol-5-one (2a) was used as starting material which was prepared via the reaction of glycine with p- nitro benzoyl chloride in presence of NaOH followed by the reaction with benzaldehyde in the presence of acetic anhydride and fused sodium acetate the reaction was confirmed by further preparation via the reaction of compound (1) with N, N dimethyl benzaldehyde which yield compound 4-(4-N,N-dimethyl benzyliden) 2-(4-nitro-phenyl)- oxazol-5-one (2b) (scheme 1). Treatment of 4-benzyliden-2-(4-nitro-phenyl)4H-oxazol-5-one (2a) with p-amino phenol afforded 4-benzyliden -1-(4-hydroxy-phenyl-2-(4-nitro phenyl) imidazol-5 one (3).

Keywords

Oxazoline, Heterocycle, Cyclization, Dehydrating Agents, Heat

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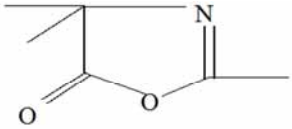
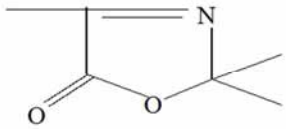
1. Introduction

There are five possible types of oxazolones. Their skeletal formula and names are given as follow:



5(4H)2-Oxazolin-5-one

A



5(2H)3-Oxazolin-5-one

B

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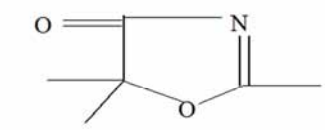
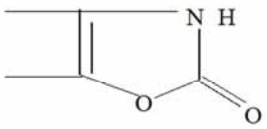


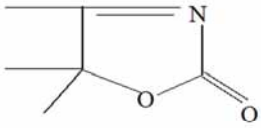
4(5H)2-Oxazolin-4-one

C



2(3H)4-Oxazolin-2-one

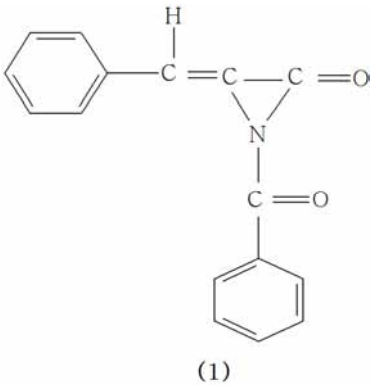
D



2(5H)3-Oxazolin-2-one

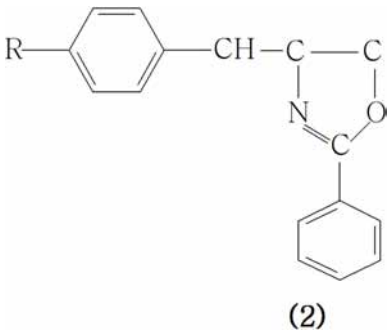
E

the largest and most important one is 5(4H)2-oxazolin-5-one (A). In 1889 [1] it was reported that heating of benzaldehyde with hippuric acid in acetic anhydride gives α-lactam structure which was called lactimide of α-benzamido-cinnamic acid (1)



(1)

in 1893, Erlenmeyer [2] accepted this structure, after that [101] he proposed the general molecular formula of oxazolones (2) which was called the aziactone of α-benzamidocinnamic acid.



(2)

The other known types are few as 5(2H)3-oxazolin-5-one (B) and 2(3H)4-oxazolin-2-one (D), but one doubtful is in 4(5H)2-oxazolin-4-one (C) and 2(5H)3-oxazoline-2-one (E) was not explored.

The work in this research is partly concerned with the synthesis of 2-oxazolin-5 ones.

1.1. Synthesis of 2-Oxazolin-5 Ones

Although 4-arylidene-2-phenyl-2-oxazolin-5 ones (2) were reported more than a century ago [3], several methods for the preparation of this oxazolones were tested and it can be summarized as the following:

1.2. Cyclization of a-Acylaminoacids

Preparation of 5(4H) 2-oxazolin -5-ones by cyclization of α-acylamino acids has more than one method shown below:

1.3. The Action of Heat

The 5 (4H) 2-oxazolin-5 ones were first isolated by Mohr and his collaborators [4, 5] by dehydration of α-acylamino acids by the action of heat as α-benzamido cinnamic acid which gives 4-benzylidine 2-phenyl-2-oxazolin-5 one on pyrolysis [2, 6]

Arylaldehydes were reacted along with hippuric acid and subjected to microwave irradiation using dimethylacetamide as a suitable energy transfer solvent and dicyclohexylcarbodimide as a condensing agent [7, 8, 9], time takes not more than 1.5-2.0 mm. without affecting the phenolic hydroxyl groups and provide excellent yields of the corresponding 4-arylidene-2-phenyl-2-oxazolin-5-ones (2).

1.4. The Action of Dehydrating Agents

Using dehydrating agents such as acetic anhydride [3, 10] or acid chloride [11], benoyl chloride in pyridine [3] or phosphorus tribromide [12], and other reagents of similar types at about 100°C or sometimes at room temperature, for treating α-acylamino acids (3) were one of the more frequently methods for preparing oxazolones. If the oxazolone is sufficiently stable to hydrolysis, it is removed by decomposing the acetic anhydride with an excess of water otherwise, the reagent and acetic acid must be distilled under vacuum before crystallization of the product.

4-Arylmethylene-2-substituted-2-oxazolin-5-ones (2) were generated in benzene by cyclizing substituted α-acylamino acids (3) with benzenesulfonyl chloride in the presence of triethylamine [13], or on reaction with substituted aldehydes. It can be also prepared from N-benzoyl-α-amino acids and diethylcarbonate [14]

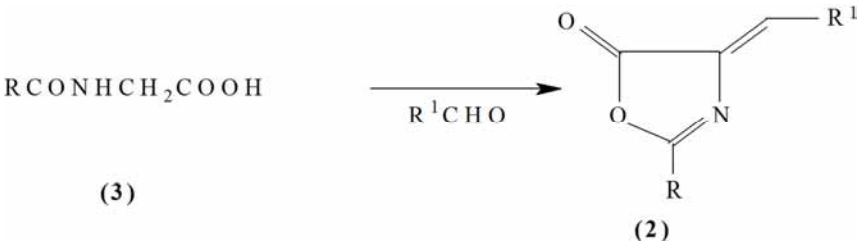


Table 1. Substituted groups on oxazoline ring.

R	R^1
a: ph	Ph
b: Me	Ph
c: ph	4-MeC_6H_4
d: ph	4-$MeOC_6H_4$
e: ph	4-$EtOC_6H_4$
f: ph	4-C_3C_6T-L
g: ph	phCH=CH
h: ph	OH, 4-NMe2ph
i: ph	3-OMe, 4-HOC_6H_4,OEt
j: ph	2-Furyl
k: ph	3-$O_2NC_6H_4$
l: ph	4-$O_2NC_6H_4$
m: ph	3,4-MeO(HO) C_6H_3
n: ph	Cyclohexane
o: phCH=CH	Ph
p: Me	OH, 4-$AcOC_6H_4$
q: Me	4-$AcOC_6H_4$
r: Me	3-OMe, 4-OMe

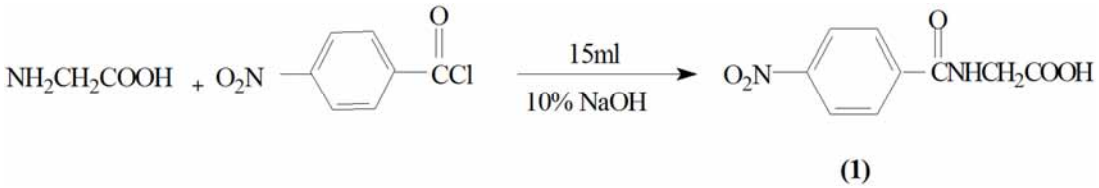
Another cyclodehydrating agent was HY-zeolite which was used for the synthesis of (2). It was impregnated with melted hippuric acid and benzaldehyde as described below [15]

2. Experimental

Melting point was uncorrected and measured by a MEL-TEML melting point apparatus. Microanalysis was performed by microanalytical laboratory, Cairo University. IR spectro were recorded with a perking Elmer 1430 ratio recording infrared spectrophotometer with CDS data station using wafer technique. H^1NMR spectra was performed on a varian Gemini (300MHz) spectrometer and mass spectra on a GC-MSQP 1000EX schmadzu. The purity of synthesized compounds was checked by TLC on glass coated plates in the laboratory with silica gel GF254 type. 60me-sh, size 50-250 in the following solvent systems S_1 choloroform/ methanol (95:5); S_2 chloroform/ acetic acid/ methanol (90:5:5). The spots on thin layer plates were detected by exposure in iodine vapor.

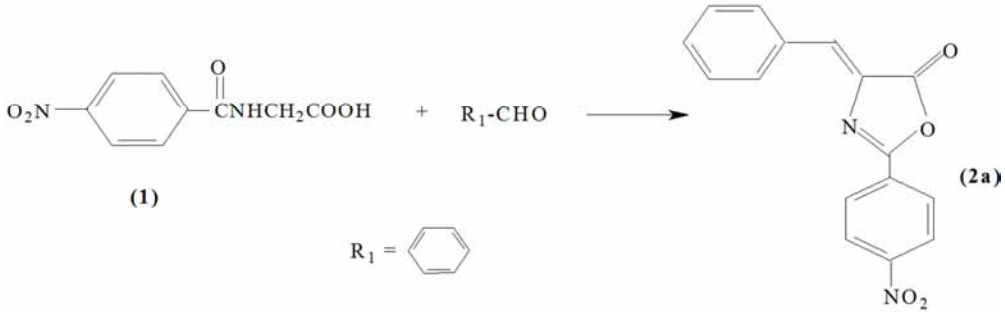
2.1. Synthesis of p-Nitro Benzoyl Amino Acetic Acid (1)

Dissolve 5g (1mol) of glycine in 10 percent sodium hydroxide solution contained in conical flask. Add 8g (1mol) of p-nitro benzoyl chloride in five portions to the solution. Stopper the vessel and shake vigorously after each addition until all the chloride has reacted. Transfer the solution to a beaker and rinse the conical flask with a litter water. Place a few grams of crushed ice in the solution and add concentrated hydrochloric acid slowly and with stirring until the mixture is acid to Congo red paper. Collect the resulting crystalline precipitate of p-nitro benzoyl amino acetic acid. The resulting solid was filtered off, washed with water, dried and rectystallized from proper solvent (water) to give compound (1) m.p 132°C, white yellow color.



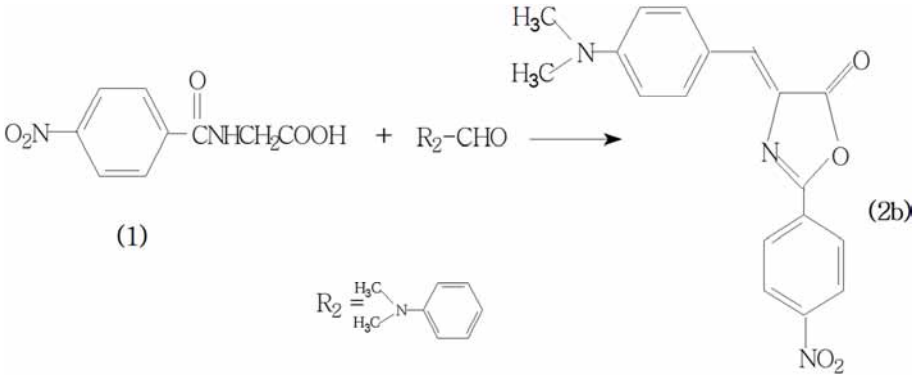
2.2. Synthesis of 4-Benzyliden-2-(4-Nitro-Phenyl)-4H-Oxazol-5-One (2a)

A mixture of 2.2g (0.01mol) p-nitro benzoyl amino acetic acid and 4ml benzaldhyde in 20 ml of acetic anhydride in the presence of fused sodium acetate (1g) was heated under reflux for 4hrs, the reaction mixture was cooled poured into water, the resulting product was filtered off. Washed with water, dried and recrystallized from proper solvent (ethanol) to give compound (2a) m.p 235°C, yellow color.



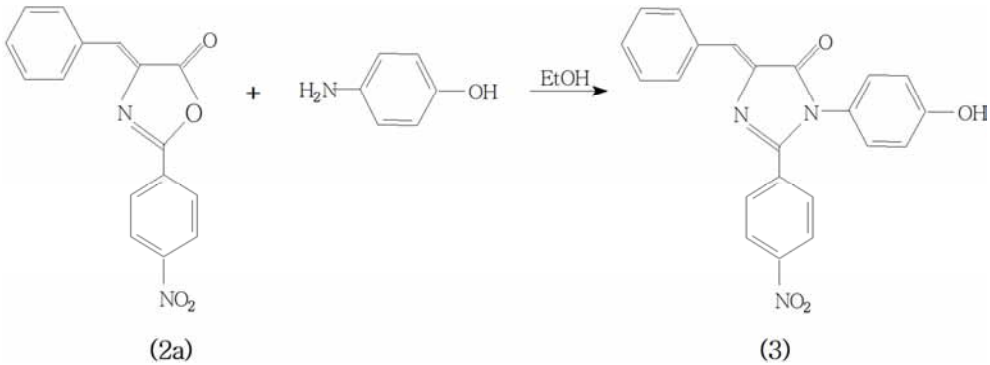
2.3. Synthesis of 4-(4-N,N-di Methyl Benzyliden) 2-(4-Nitro-Phenyl)-Oxazoline-5-One (2b)

A mixture of 2.2g (0.01mol) p-nitro benzoyl amino acetic acid and 1.4g (0.01mol) N,N-di methyl benzaldhyde in 20 ml of acetic anhydride in the presence of fused sodium acetate (1g) was heated under reflux for 4hrs, the reaction mixture was cooled poured into water, the resulting product was filtered off. Washed with water, dried and recrystallized from proper solvent (ethanol) to give compound (2b) m.p 175°C, grey color.



2.4. Synthesis of 4-Benzyliden-1-(4-Hydroxy-Phenyl-2-(4-Nitro Phenyl)-Imidazol-5-One (3)

A mixture of 2.9g (0.01mol) compound (2a) and 3.8g (0.01mol) p- amino phenol in 20ml acetic acid was heated under reflux for 6hrs, the reaction mixture was cooled and poured into water, the resulting solid was filtered off. Washed with cooled water, dried and recrystallized from proper solvent (ethanol) to give compound (3) m.p 242°C, brown-yellow color.



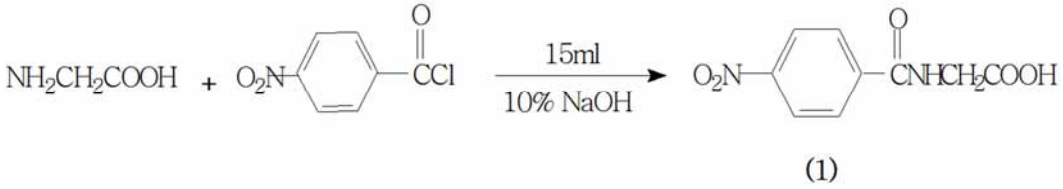
3. Result and Discussion

The use of oxazolone compounds as starting materials for the preparation of heterocycles were proved by many papers but their uses are still explored and some of their wide application for industrial and biological fields were shown.

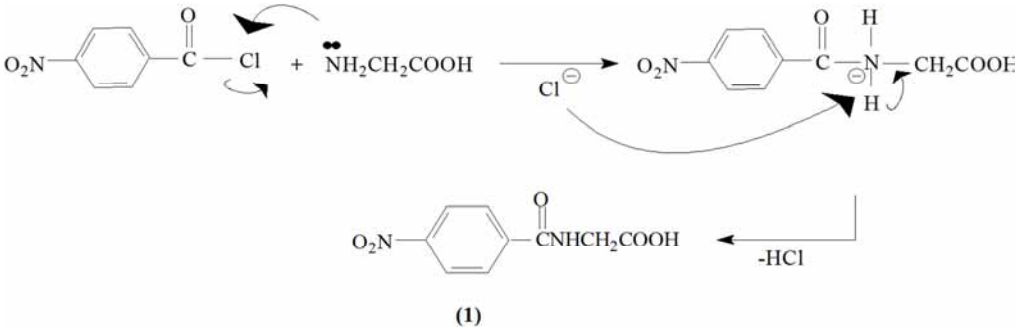
The oxazolone derivatives are reported to exhibit biological activity such as anticancer activity, used as substrates in active site of hydrolysis and its antibacterial site action or antimicrobial activity.

3.1. Synthesis of p-Nitro Benzoyl Amino Acetic Acid (1)

The author tends to synthesize substituted p-Nitro benzoyl amino acetic acid (1) via the reaction of glycine with p-Nitro benzyl chloride.



The formation of p-Nitro benzoyl amino acetic acid (1) take place via the following mechanism as shown in (Scheme 4).



The IR spectrum of (1) showed stretching vibration frequencies attributable for the carbonyl group (C=O) at υ (1745 cm^{-1}), and at υ (1489-1408 cm^{-1}) for (NO_2) group, at υ (3113-3053 cm^{-1}) duo to stretching frequency of the (-NH) group, at υ (3342 cm^{-1}) duo to stretching frequency of (-OH) group, at υ (1600cm^{-1}) for (C=C) group. Figure 1.

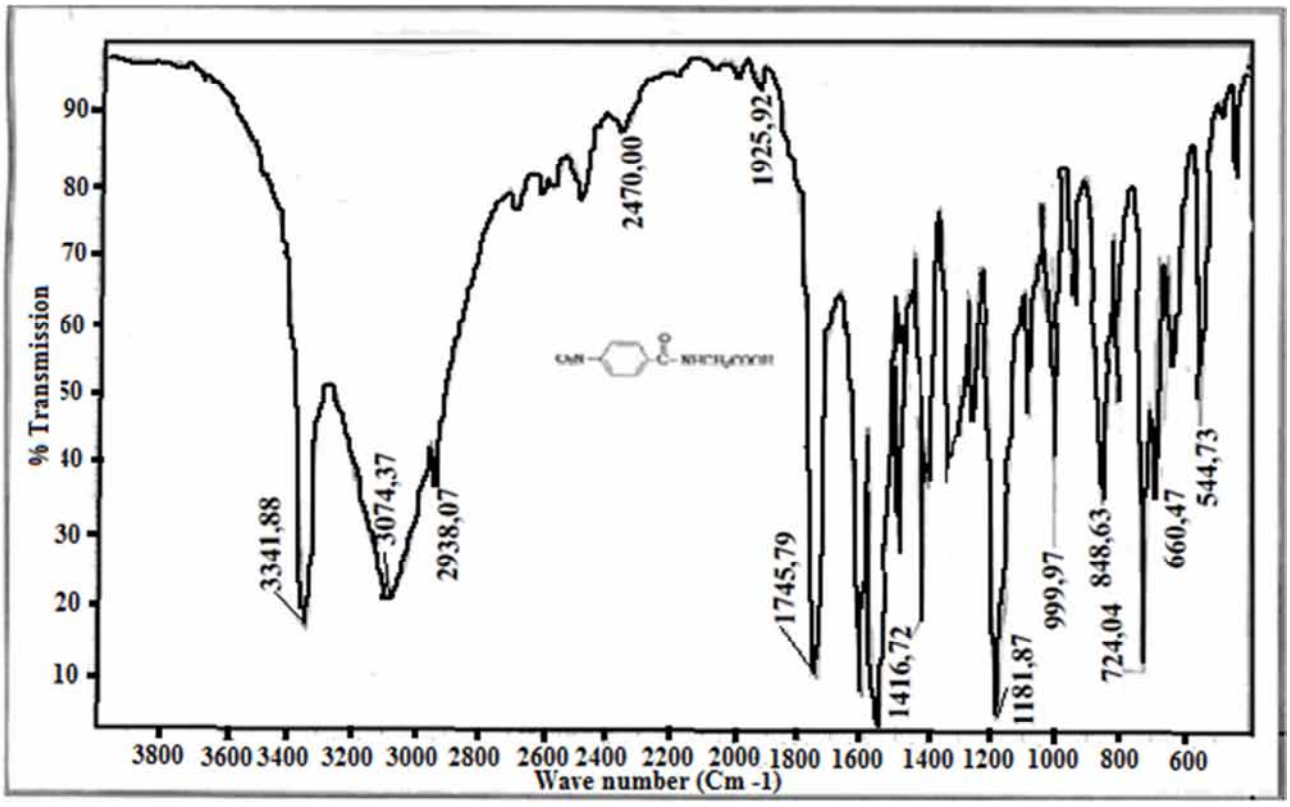


Figure 1. IR Spectrum of Compound (1).

The mass spectrum additional confirmation for the structure (1) shows a molecular ion at m/z =224 representing the molecular weight Figure 2 the molecular modolling of (1) are shown in Figure 3.

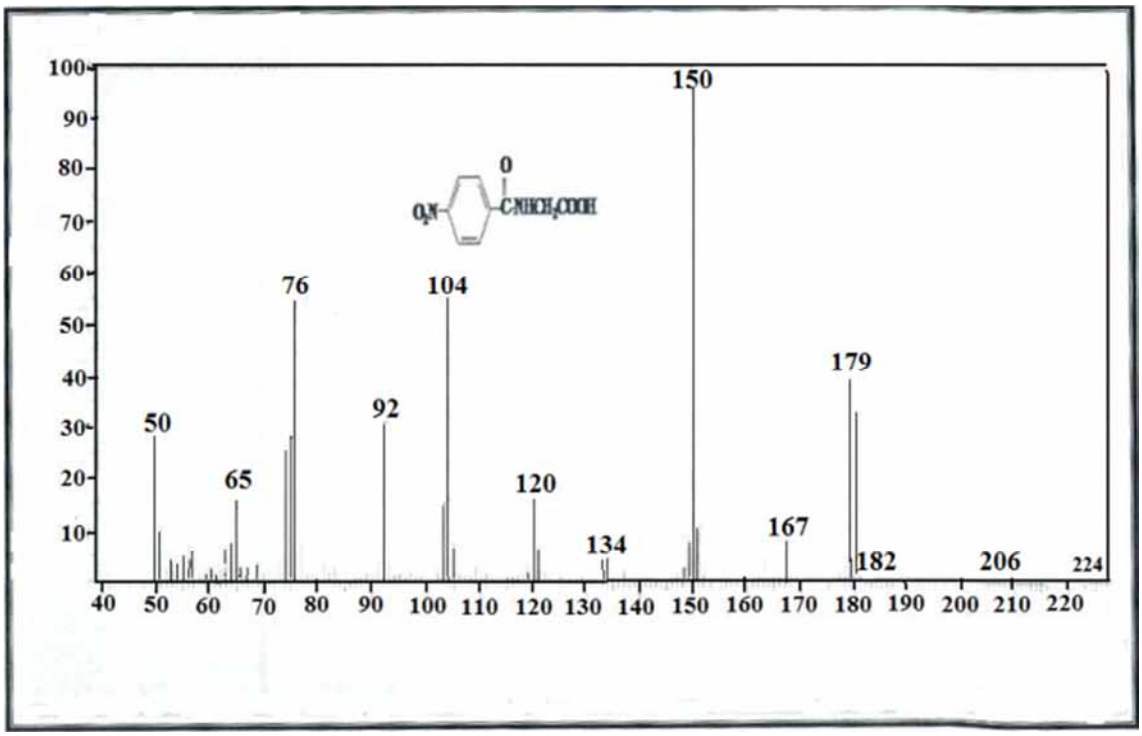


Figure 2. Mass spectrum of compound (1).

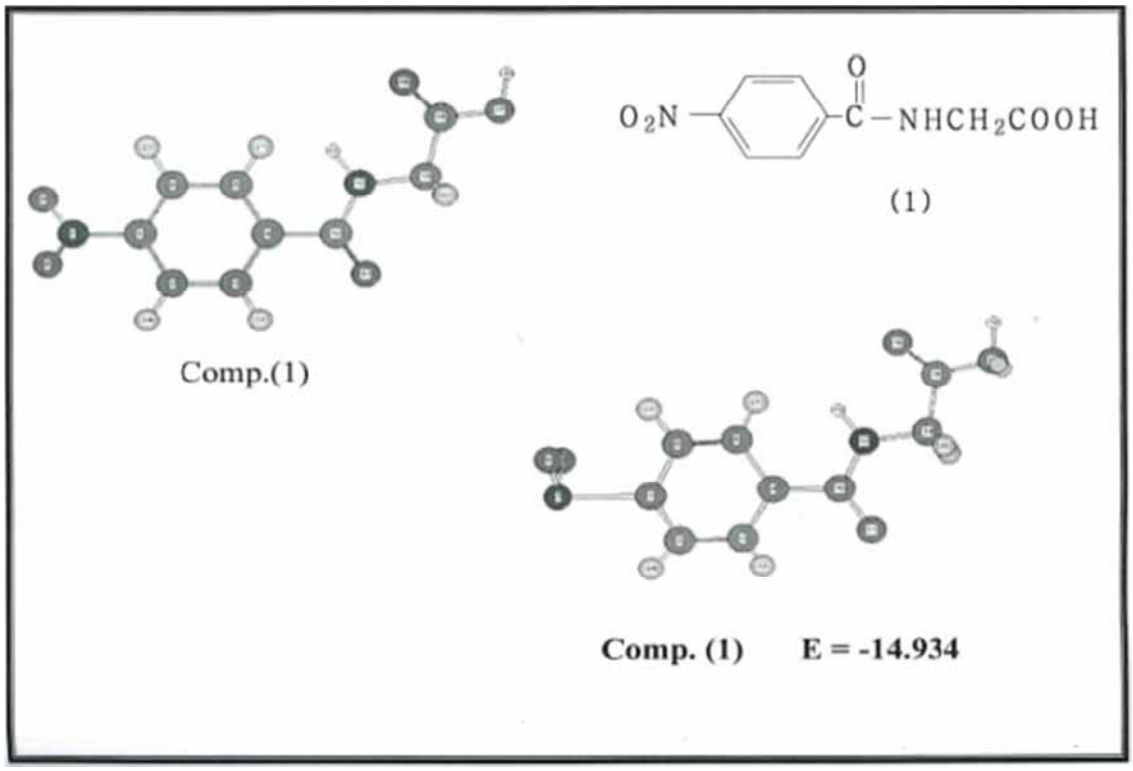
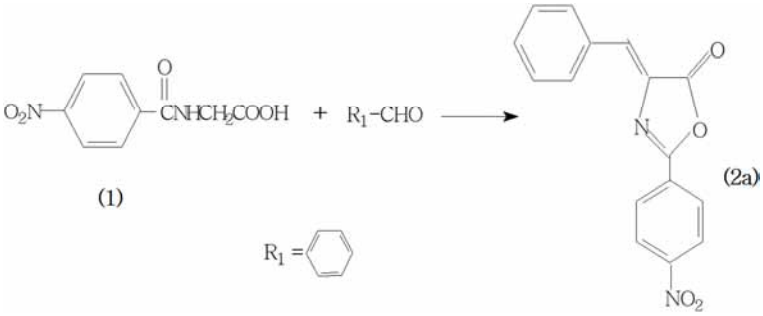


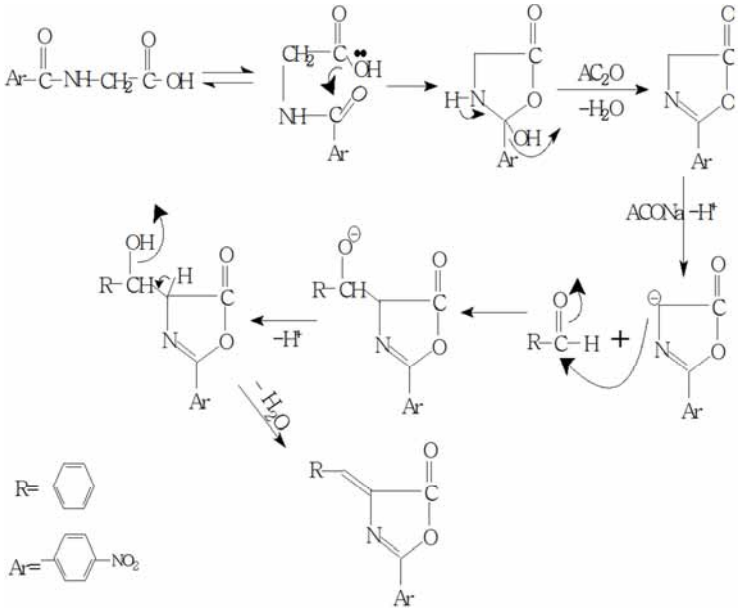
Figure 3. Molecular Modolling Of compound (1).

3.2. Synthesis of 4-Benzyliden-2-(4-Nitro Phenyl)-4H-Oxazol-5-One (2a)

Treatment of p-Nitro benzoyl amino acetic acid (1) with benzaldehyde under reflux yielded the corresponding 4-benzyliden-2-(4-nitro phenyl)-4H-oxazol-5-one (2a)



The reaction of p-Nitro benzoyl amino acetic acid (1) with benzaldehyde possibly takes place according to the following mechanism as shown in (Scheme 5).



The IR spectrum of (2a) showed absorption bands at υ (3067cm^{-1}) for (CH aromatic), at υ (1690 cm^{-1}) for (C=O) group for (C=C) group at υ (1600cm^{-1}), at υ (1542 cm^{-1}) for (C=N) group, and at υ (1428 cm^{-1}) for (NO_2) group) Figure 4.

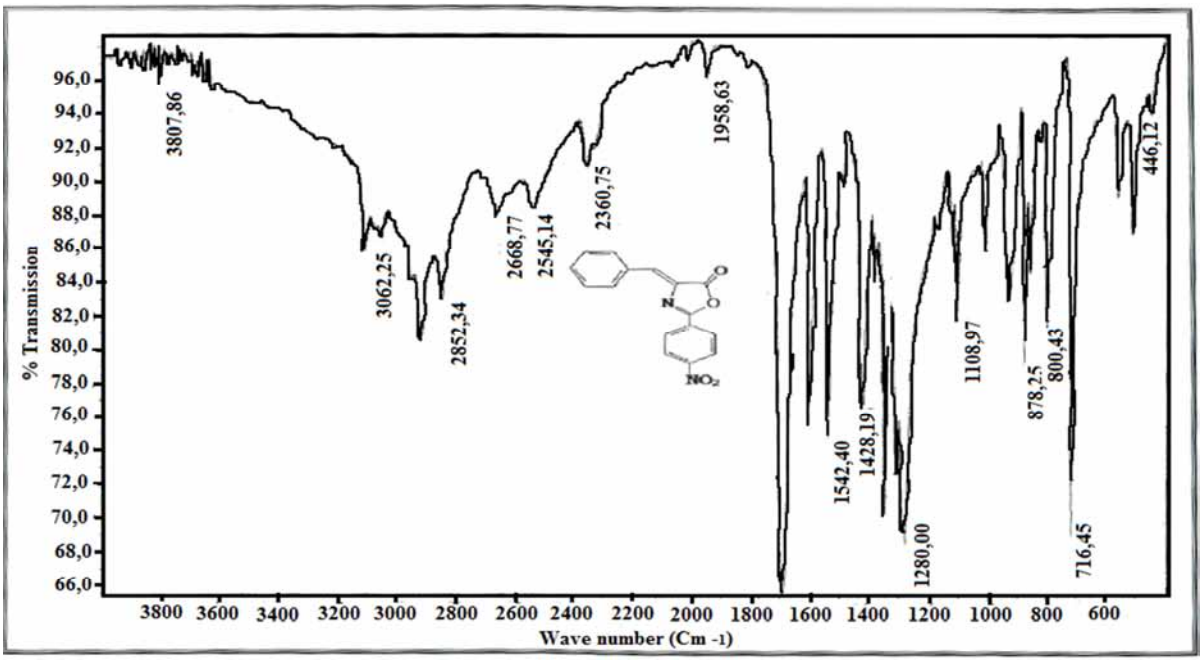


Figure 4. IR spectrum of compound (2a).

The mass spectrum of (2a) adds a good additional confirmation for the suggested structure and showed a molecular ion peak at m/z = 294 representing the exact molecular weight of compound (2a); Figure 5.

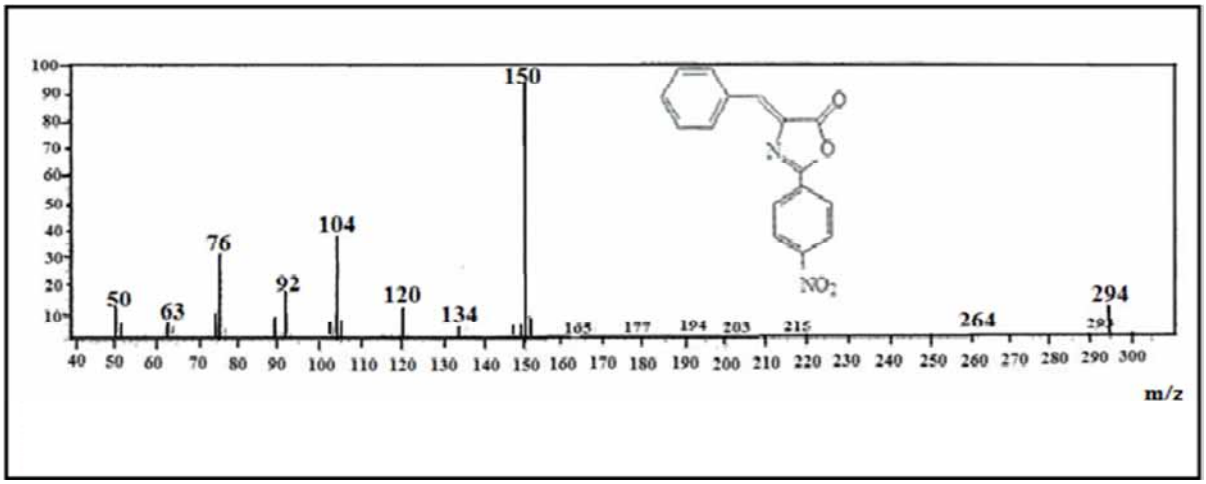
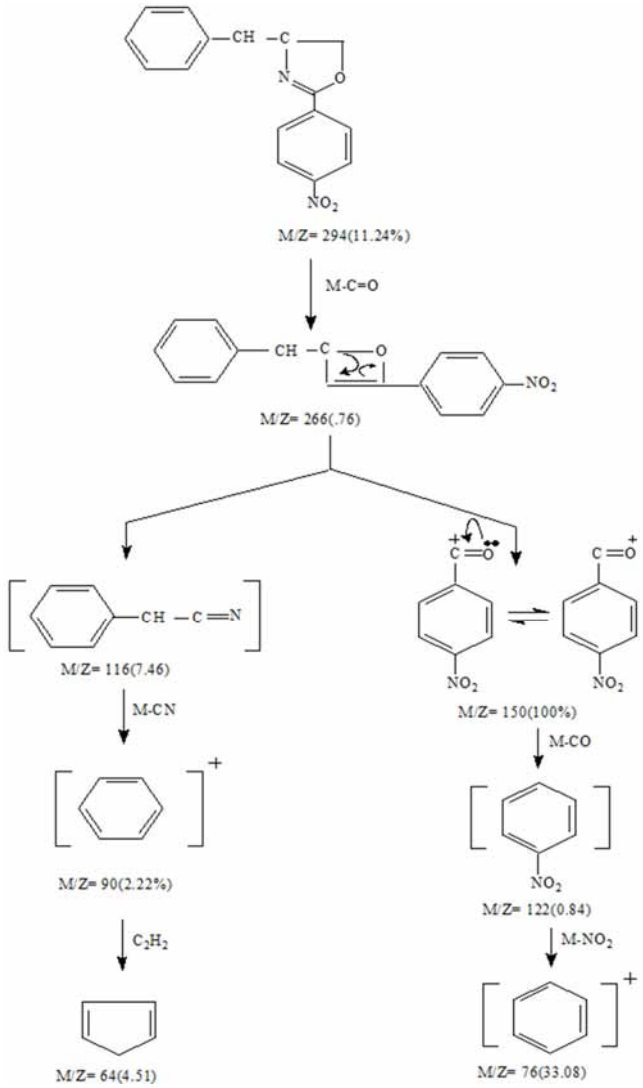


Figure 5. Mass spectrum of compound (2a).



The molecular modolling of compound (2a) are shown in Figure 6.

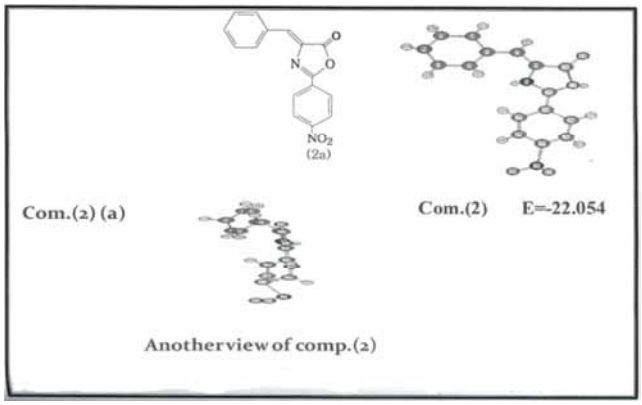
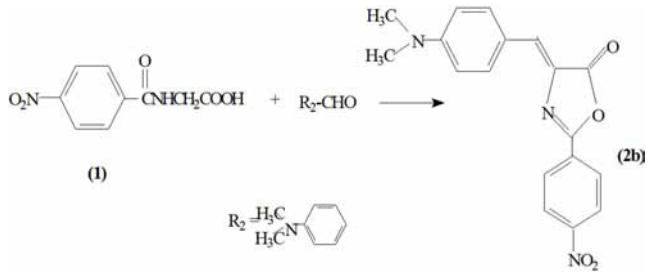


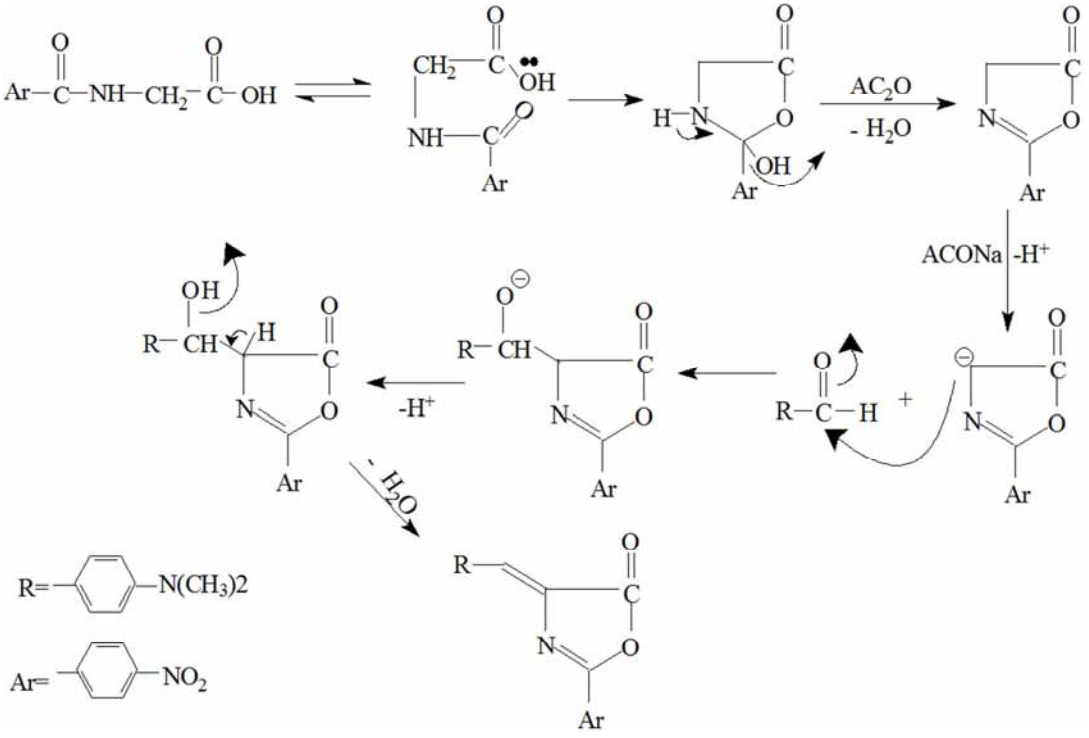
Figure 6. Molecular Modolling of compound (2a).

3.3. Synthesis of 4-(4-N,N-di Methyl Benzyliden)2-(4nitro Phenyl)-Oxazoline-5-One (2b)

Also the reaction of p-Nitro benzoyl amino acetic acid (1) with N,N-di methyl benzaldehyde under reflux afford 4-(4-N,N-di methyl benzyliden)2-(4nitro phenyl)-oxazoline-5-one (2b).



The reaction of p-Nitro benzoyl amino acetic acid (1) with N,N-di methyl benzaldehyde possibly takes place according to the following mechanism as shown in (Scheme 4).



The IR spectrum of (2b) showed absorption bands at υ (3062cm^{-1}) for (CH aromatic), at υ (2853cm^{-1}) for (CH aliphatic), at υ (1690 cm^{-1}) for (C=O) group, for (C=C) group at υ (1600cm^{-1}), at υ (1542 cm^{-1}) for (C=N) group, and at υ (1428 cm^{-1}) for (NO_2) group) Figure 7.

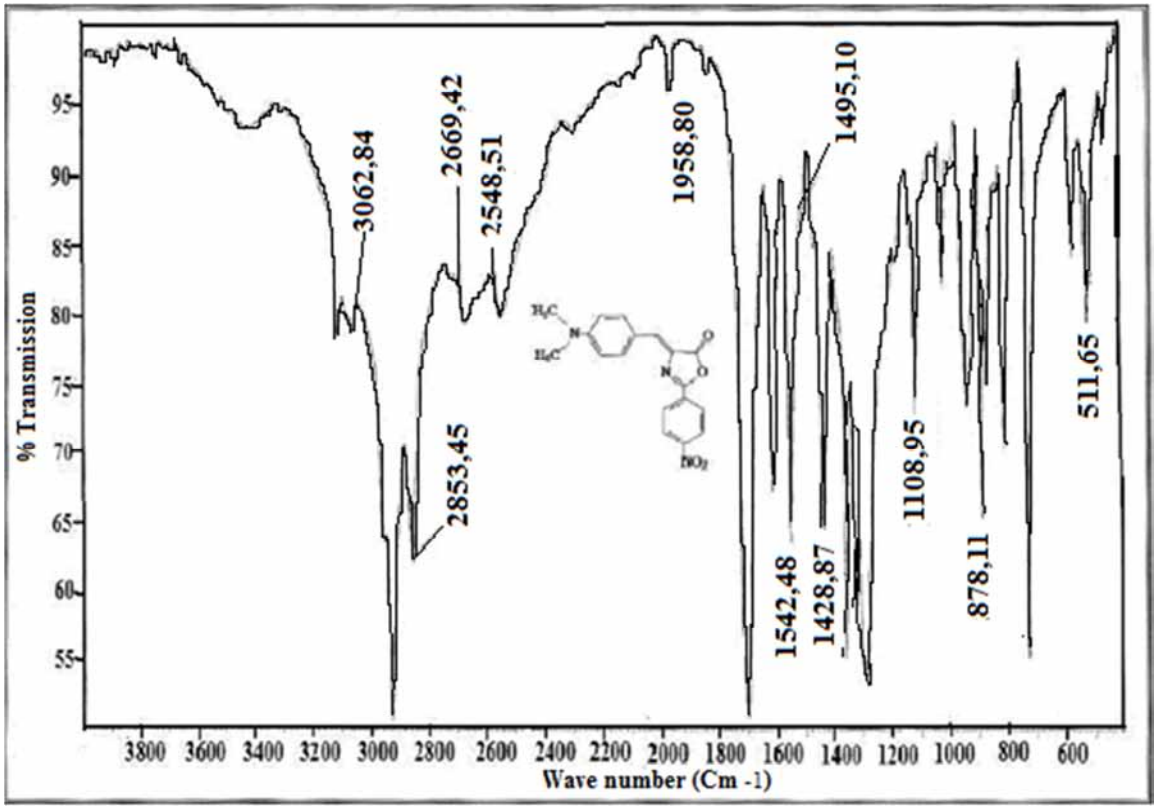


Figure 7. IR spectrum of compound (2b).

The mass spectrum of (2b) adds a good additional confirmation for the suggested structure and showed a molecular ion peak at m/z = 332 representing the exact molecular weight of compound (2b); Figure 8.

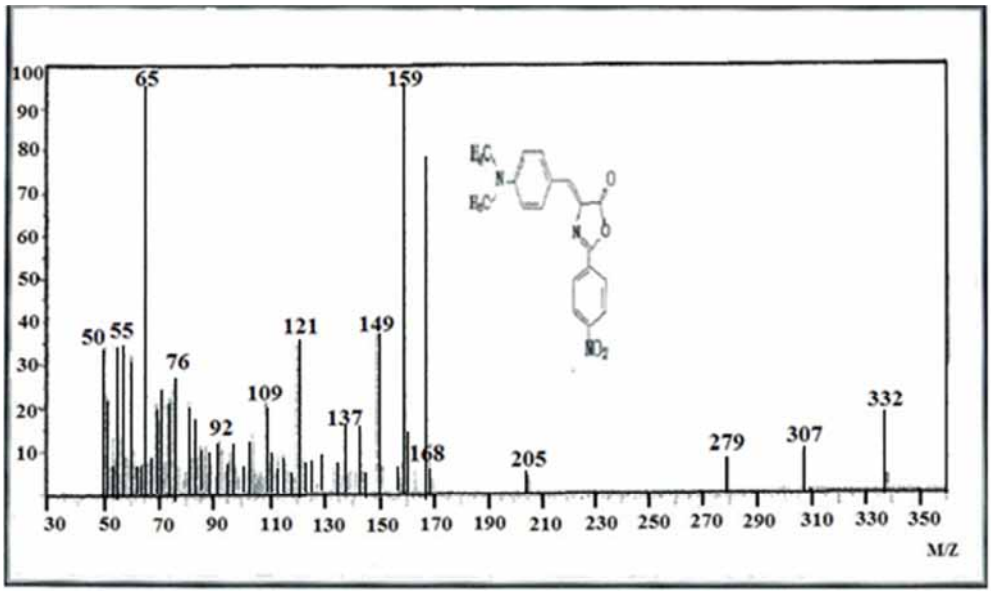
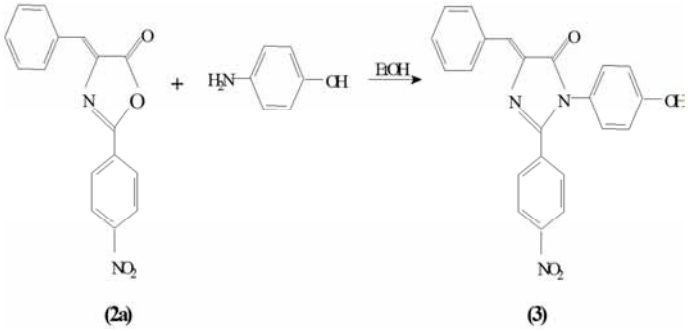


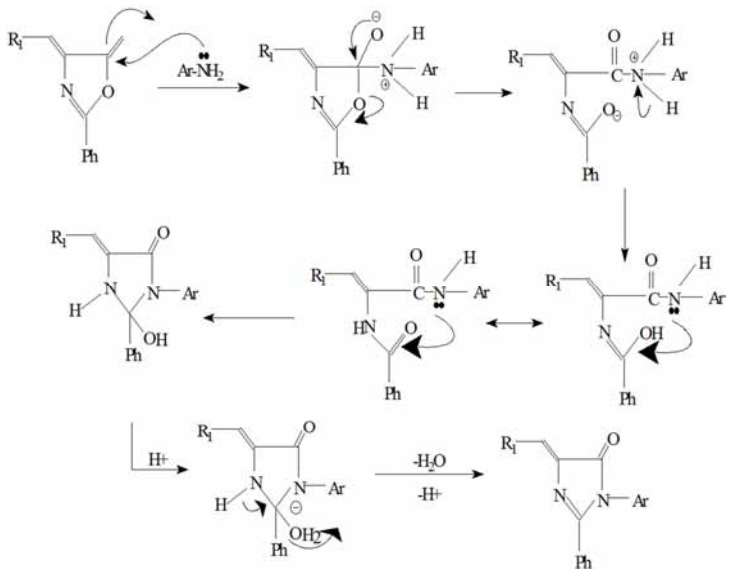
Figure 8. Mass spectrum of compound (2b).

3.4. Synthesis of 4-Benzyliden-1-(4-Hydroxy-Phenyl-2-(4-Nitro Phenyl)-Imidazol-5-One (3)

Also the reaction 4-benyliden-2-(4-nitro phenyl)-4H-oxazol-5-one (2a) with p-amino phenol under reflux afford 4-benzyliden-1-(4-hydroxy-phenyl-2-(4-nitro phenyl)-imidazol-5-one (3).



The reaction of 4-benyliden-2-(4-nitro phenyl)-4H-oxazol-5-one (2a) with p-amino phenol possibly takes place according to the following mechanism as shown in (Scheme 9).



The IR spectrum of compound (3) showed absorption bands at υ (3414 cm^{-1}) for (OH) group, at υ (3000 cm^{-1}) (CH aromatic), at υ (1763cm^{-1}) for (C=O) group, at υ (1640cm^{-1}) for (C=C) group, at υ (1523cm^{-1}) for (C=N) group and at υ (1332cm^{-1}) for (NO_2) group. Figure 9.

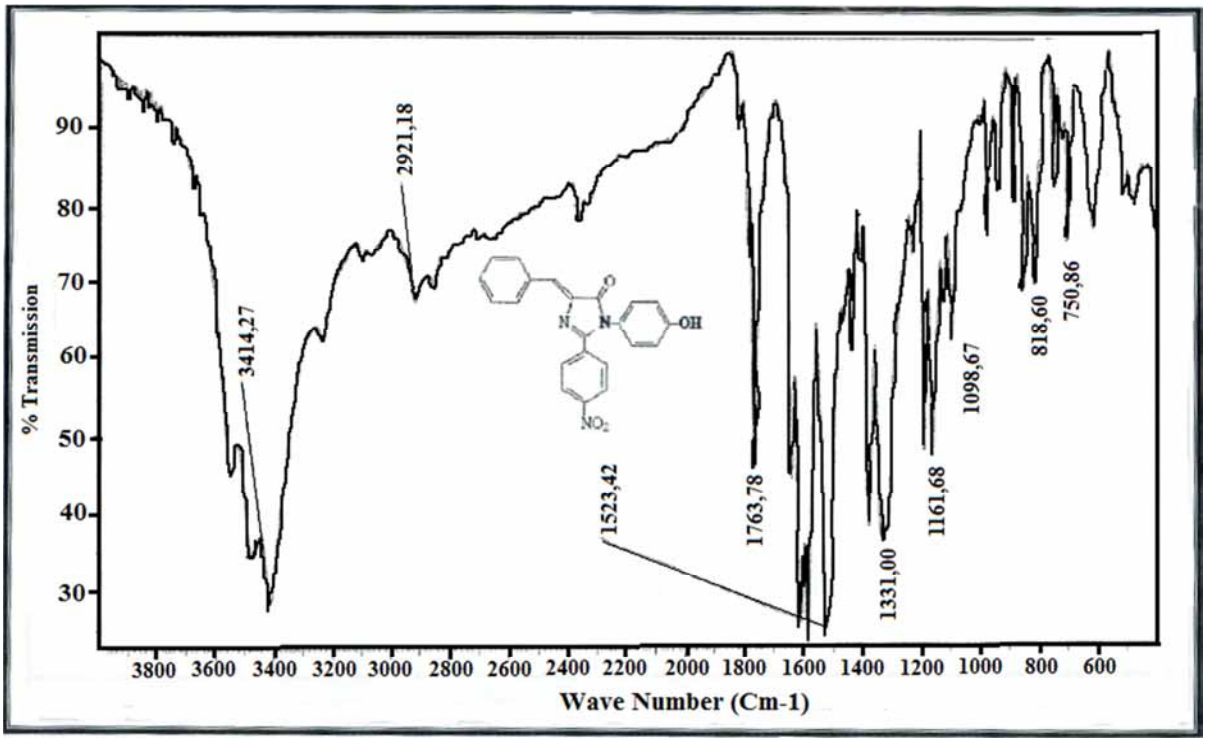


Figure 9. IR spectrum of compound (3).

The mass spectrum of (3) adds a good additional confirmation for the suggested structure and showed a molecular ion peak at m/z =385 representing the exact molecular weight of compound (3), Figure 10.

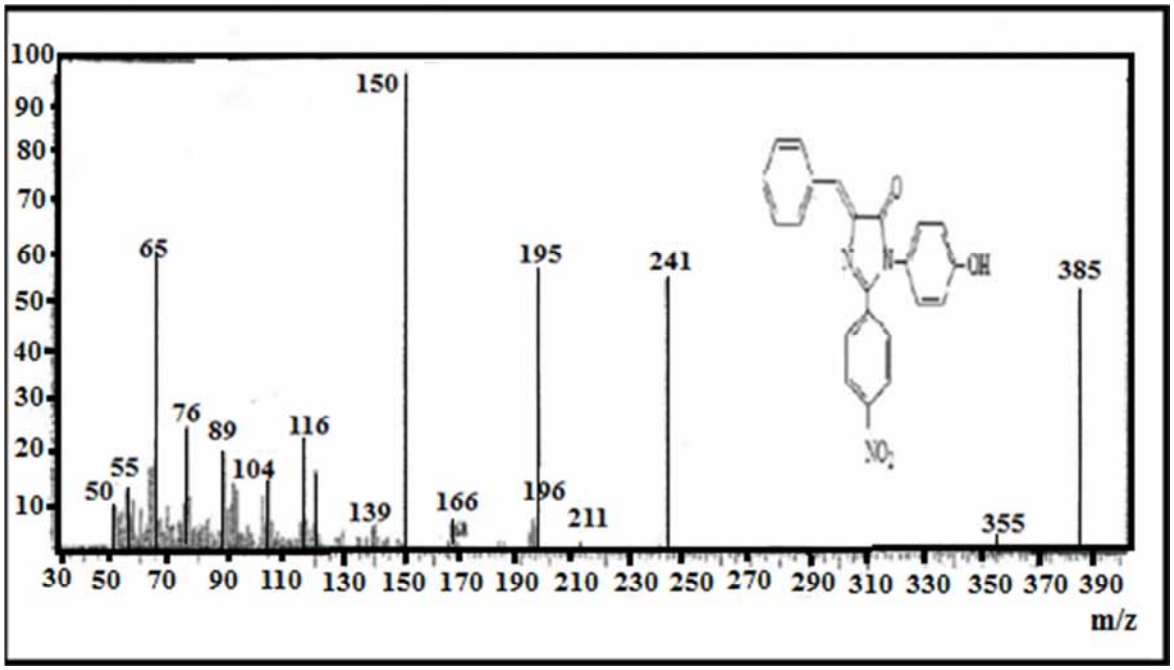


Figure 10. Mass spectrum of compound (3).

The molecular modelling of compound (3) are shown in Figure 11.

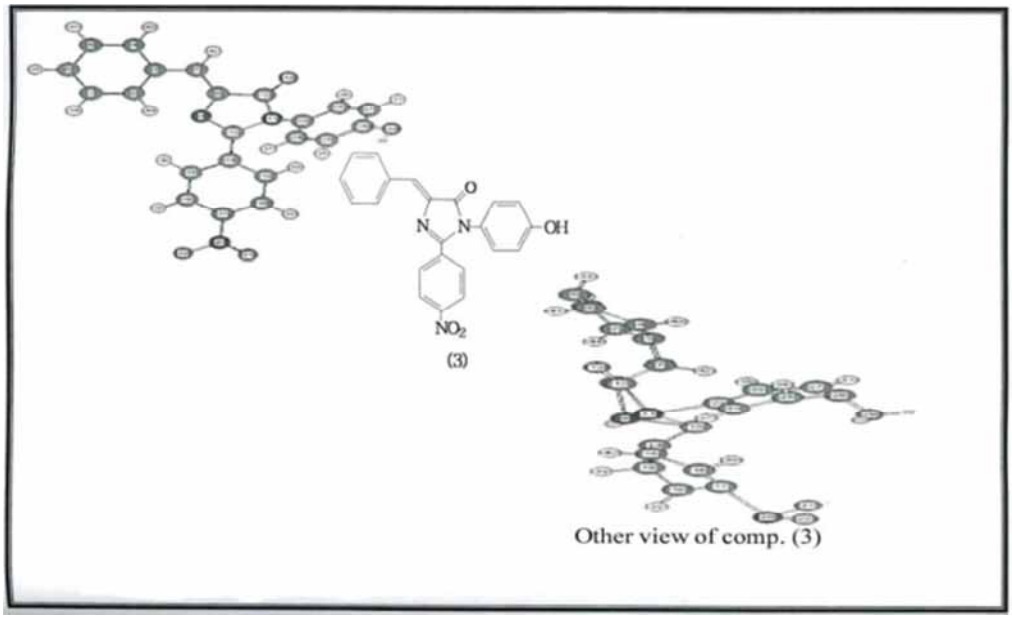


Figure 11. Molecular Modelling of compound (3).

4. Conclusion

|In recent years heteocyclics received great attention. In heterocyclic chemistry oxazoline is one of the most important moiety. Oxazoline moiety shows a wide range of application such as in agriculture industry, pharmaceutical, food industry, natural product, medicine, polymers and various other industries. Oxazoline moiety constitutes the core structure of many biologically active natural compounds. Oxazoline play a major role in medicinal chemistry. Heterocyclic compounds whose containing oxazoline moiety as core structure reported wide range of biological activities such as antibacterial, antifungal, antimicrobial, antioxidant, antipyretic, anti-HIV, anti malarial, anti tumour, anti viral, anti-inflammatory, CNS stimulant activity etc. Oxazolines synthesized by the reaction of various aromatic substitutes like acids, aldehydes, nitriles, azides etc. Synthetic chemist do great work on the synthesis and application part of oxazolines.

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