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Reaction of oxazoloneswith 5, 5'-methylenebis(2-aminopyridine)

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Abstract: *4-arylidene-phenyl/methyl oxazolone have been synthesized from reactions of various aromatic aldehydes such as benzaldehyde (3a), 4-chlorobenzaldehyde (3b), 4-hydroxybenzaldehyde (3c) and 4-methoxybenzaldehyde (3d) with hippuric acid and acetyl glycine in the presence of anhydrous sodium acetate with acetic anhydride as a basic medium.Treatment of produced oxazolones with 5,5 methylene bis (pyridine-2-amine) which was prepared during this work by reacting 2-amino pyridine with formaldehyde to give ethyl acet /benz amide acrylate (I-VIII).In addition,All the synthesized compounds were identified on the basis of m.p, TLC, IR, 1H NMR, D2O Exchange, 13C NMR, APT spectroscopy*.

Key words:*hippuric acid, acetyl glycine, oxazolone, bis(pyridine-2-amine), acrylate.*

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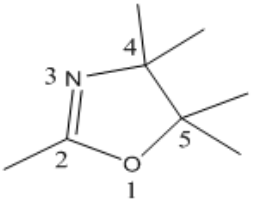
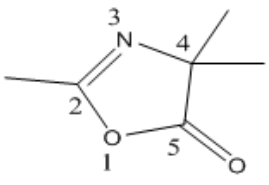
I. Introduction

Oxazolones are heterocyclic compounds that perform an important role in the synthesis of several organic molecules including amino acids, amino alcohols, thiamine, amides, peptides, and polyfunctional compounds. Certain natural and synthetic oxazolones also including benzoxazolone derivatives possess important biological activities such as antimicrobial, anti-inflammatory, anticancer, anti-HIV, anti-angiogenic, anti-convulsant, anti-tumor, sedative, and cardiotonic activity. (Mesaik et al. 2004& Tikdariet al. 2008). Oxazolones exhibited promising photophysical and photochemical activities and also were used in semiconductor devices such as electrophotographic photoreceptors and non-linear optical materials. Oxazol-5-ones also known as azlactones, are readily prepared from N-protected amino acids by dehydration (Gottwald& Seebach 1999). Ring-opening of oxazolone leading to enriched N-protected phenylalanine ester and peptido-alcohols oxazolone linked to the structure and chemistry of penicillin. Oxazolones show interesting behavior toward polymerization, condensation reagents, herbicides, fungicides, pesticides and agrochemical intermediates (Abdel-Aty, 2009). Substitution functional group at C-4 and C-2 position as shown in (a) (b), plays a vital role in the activity of the oxazolone. Substituted (p-nitro) exocyclic phenyl group at C-4 of oxazolone moiety greatly influences the immunosuppressive activity. Cinnamoyl residue at C-4 of oxazolone moiety and substitution of a functional group at C-4 and C-2 positions of oxazolone are crucial for tyrosinase inhibitory activity. An extension of conjugation through an aliphatic double bond present at the C-4 position of oxazolone moiety and a phenyl ring present at C-2 play a pivotal role in activity (Khan et al. 2006). The rate of the oxazolone ring-opening reaction decreased with an increase of the electron- donating properties of the substituted of the phenyl ring at -2-position.(Betlakowska et al. 2002). The exocyclic double bond can operate a dienophile and N-substituted oxazolone participate in intermolecular Deils-alderreactions (Fearnley& Market 2002).Lewis acid activation of the carbonyl group of unsaturated oxazolone gives electrophilic character to the β-carbon. The positive charge of carbon C-2 increase by m- NO_2 group which may be easily attacked by any nucleophile, an alkoxy group at the para position of the phenyl ring decrease the negative effect of the nitro group and the electron-withdrawing effect of this group may support the attack of the (C=N) group. The bond order of the C=N group decreases by the presence of the m-Nitro group at the benzylidine ring(Bala et al. 2011).

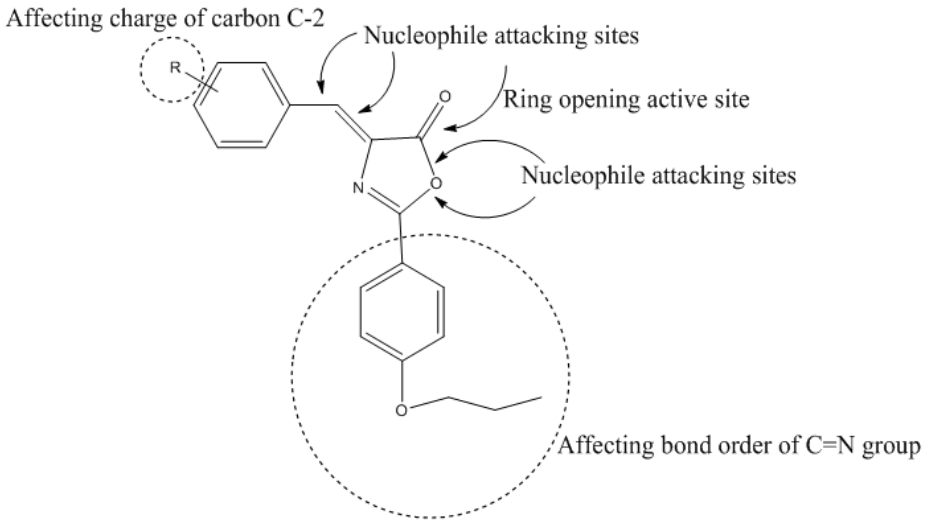


(a)

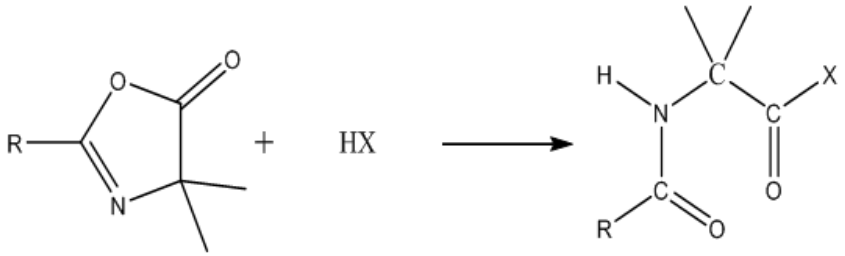


(b)

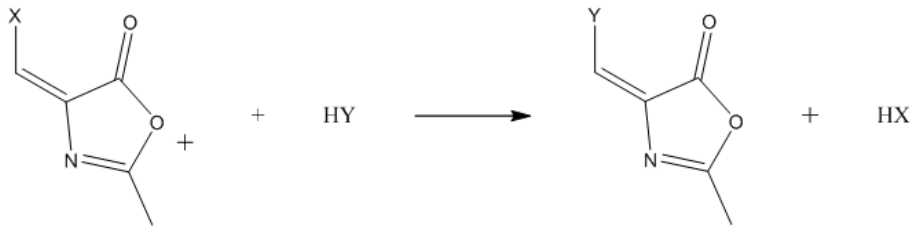
The 5(4H) oxazolones have several electrophilic centers as shown (Bala et al. 2011).



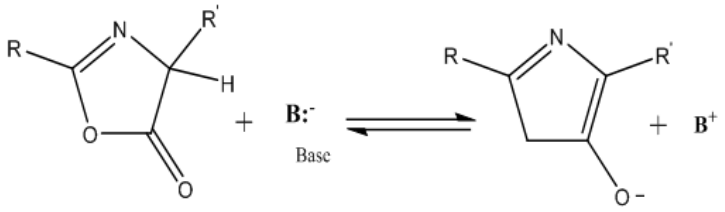
In their reaction with nucleophilic reagent, the 5(4)-oxazolones behave for the most part like acid anhydride to which they have a structural resemblance. the electron attracting influence of the C=N group prevents the attached oxygen atom from deactivating to any great extent, the 5-carbonyl group. This group is, therefore, like ketonic carbonyl rather than a lactone carbonyl and has astrong attraction for nucleophilic reagents. water, acid, alcohols, thiols, amines and the like usually attack this electrophilic C-5 center and the tendency of a ring to open with the formation of the stable amide grouping often makes this attack irreversible. These reactions can be given a general representation which sums up a large part of oxazolones chemistry.



However, the 5(4H)-oxazolones also contain an imino ether structure for which C-2 is another potential target for nucleophilic agents and occasionally attacked before C-5 carbonyl carbon. The 4-alkylidene-5(4)-oxazolones are more stable than their saturated analogs and this lower internal energy is reflected in their greater ease of formation. The reactivity at C-5 is diminished, although still predominant and there is an additional electrophilic center on the exocyclic double bond (C-4).Instances in which addition occurs at this center are difficult to identify, as the resulting saturated and less stable oxazolone undergoes further reaction. The 4-heteromethylene-5(4)-oxazolones are substances in which the addition of nucleophilic reagent to the exocyclic double bond can be followed by the elimination of hetero anion X (where X= -OH, -OR, -SR, etc.) to produce another "hetero methylene oxazolone" of similar energy content. In these compounds, this displacement reaction can compete with and often takes precedence over the reaction at C-5.



High mobility of hydrogen at C-4 is another feature of oxazolone chemistry. This is probably due to the stabilization of the anion by resonance as an oxazole.



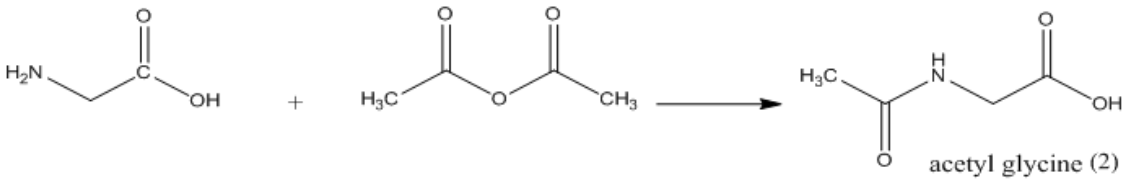
The anion is a highly reactive nucleophilic reagent. Its reaction withaldehydes, ketones, acetals, acid anhydrides, amides, amidines constitutes, in all probability, the essential stage of the Erlenmeyer synthesis and involves an addition to an electrophilic center (reaction with carbonyl compounds) or displacement of another anion (reaction with acetals and ethyl orthoformate).In the present work, we aimed to study the action of nitrogen nucleophiles on 4-Arylidene-2-phenyloxazol-5(4H)-one (4 a,b,c, and d) and 4-Arylidene-2-methyloxazol-5(4H)-one (5 a, b, c, and d) under different conditions hoping to obtain new heterocyclic compounds imidazolonerings through the opening and recycling the oxazolone ring**.**

II. Materials and methods

Materials: All chemicals were purchased from Sigma-Aldrich (St. Louis, Mo, USA)and were used as received.Reactions were monitored on TLC(Diethyl ether/chloroform). All spectroscopic analysis of prepared compounds were conducted at the microanalytical center of South Africa, Cape Town University. ^{1}H NMR spectra were carried out on Bruker 300 MHz with chemical shift (δ) expressed in ppm downfield from tetramethylsilane as an internal stander (δ MS=0) usingCDCl3 as a solvent. The multiplicity of the signal is as follows: s (singlet), d (doublet), t(triplet), q(quartet), m(Multiplet).^{13}C-NMR were measured on Bruker 75 MHz with internal reference TMS δ=0.Infrared spectra were recorded on Maltson 5000 FT IR spectrometer on Perkin Elmer model spectrum100, where the positions of absorptions have been expressed in wavenumber units (cm^{-1}).Melting points (m.p) of the synthesized compounds were measured in capillary tubes using theGriffin apparatus and are uncorrected.

Methods:

Preparation of acetyl glycine (2):



In a round-bottomed flask 50 ml glycine (12.5 mmol) was dissolved in 5 ml distilled water, then (25 mmol) of acetic anhydride was added in one portion with stirring for 15-20 minutes. The reaction mixture was cooled on an ice bath, filtered and washed with cold water. The crude product was recrystallized from water dried under reduced pressure to give 49% yield with m.p 204-206 C°.

Synthesis of starting material (Oxazolones) (Scheme 1)
The reaction of aromatic aldehydes with acetyl glycine (5a, b, c, and d**)**

General procedure:
In a round-bottomed flask (47 mmol) acetyl glycine (2), aromatic aldehyde (3 a, b, c, d) (72 mmol), and anhydrous sodium acetate (122 mmol) was mixed, (106 mmol) of acetic anhydride was addedto this mixturecarefully then heated under reflux for 1 hour.The reaction mixture was cooled down overnight.Drops of cold water were added to the mixture until yellow crystals appeared.The produced precipitate wasFiltered off, recrystallizedusing chloroform,and dried in air.

Reactions of aromatic aldehydes with N-benzoyl glycine(4a, b, c, and d**)**

General procedure:
A mixture of N-benzoyl glycine (hippuric acid) (1) (1.2 mmol), aromatic aldehyde (3 a, b, c, d) (1.0 mmol), acetic anhydride (3.0 mmole) and fused sodium acetate (1.5mmole) were heated on a hot plate to liquefaction, the resulting mixture was heated on a water bath for two hours.After the reaction is completed, the mixture was cooled to room temperature and treated with ethanol. The ethanolic mixture was cooled in the refrigerator at 4°C overnight, the solid product was washed with hot water and air-dried at room temperature for two hours and then recrystallized from ethanol to give thecorrespondingazlactones.

Synthesis of 5,5'-methylenebis(2-aminopyridine) (8).

General procedure:
To a solution of 2-aminopyridine (6), (10mmol) in water (25 mL), formaldehyde (7), (5mmol) was added slowly with constant stirring for two hours. A white cream solid was precipitated which was filtered, washed with water, dried in vacuum, and recrystallized from ethanol where gave 37% yield with m.p 133-135°C.

Synthesis of products:
The reaction of oxazolones with 5,5'-methylenebis(2-aminopyridine)(I-VIII)

General procedure;
A mixture of azlactone (2000 mmol) and 5,5'-methylenebis(2-aminopyridine)(8) (1000 mmol) in 40 ml of absolute ethanol was stirred under reflux for 24 hrs. The reaction mixture was allowed to cool and the resulting solid was filtered, and recrystallized from absolute ethanol.

III. Result and Discussion

Results:
Ethyl-2-benzamido-3-phenylacrylate (I):IR (KBr) ν =3264 cm^{-1} (Ph NHC=O), 1706 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ = 1.36(t, 3H, CH_3), 4.33(q ,2H, CH_2), 7.49(m, 5H, Ar-H), 7.32(m, 5H, Ar-H), 7.73(s, 1H, NH), 7.86(dt, 1H, =CH). ^{13}C-NMR($CDCl_3$): δ =14.2(q, 1C), 61.5(t, 1C), 125.5(s, 1C) ,128(d, 1C), 130(d, 2C), 130.5(d, 1C), 131(d, 5C), 132(d,1C), 133(s, 2C), 135(s, 2C), 166(s,1C).

Ethyl-2-benzamido-3-(4-chlorophenyl) acrylate (II): IR (KBr) ν=3211 cm^{-1} (Ph NHC=O), 1717 cm^{-1}(C=O), 691,708,769 cm^{-1}(para and mono substituted aromatic).^{1}H-NMR ($CDCl_3$): δ =1.36(t, 3H, CH_3), 4.33(q, 2H, CH_2), 7.30 (d, 2H, Ar-H), 7.42 (m, 3H, Ar-H), 7.48(d, 2H, Ar-H), 7.56(s, 1H, NH), 7.86(m, 3H, =CH +Ar-H).^{13}C-NMR($CDCl_3$): δ= 15(q,1C), 62(t, 1C), 125(s, 1C), 129(d, 1C) ,130(d, 2C), 130.5 (d, 4C), 132(d, 2C), 134(d, 1C), 134.5(s, 1C), 135(s, 2C), 137(s, 1C), 166.5(s,1C).

Ethyl-2-benzamido-3-(4-hydroxyphenyl) acrylate (III): IR (KBr) ν = 3261 cm^{-1}(PhNHC = O), 1698 cm^{-1}(C=O) ,692, 771, 892 cm^{-1}(para and mono substituted aromatic). ^{1}H-NMR ($CDCl_3$): δ = 1.36(t, 3H, CH_3), 4.33(q, 2H, CH_2), 7.8(m, 1H, OH), 7.25(m, 2H, Ar-H), 7.34(ddt, 2H, Ar-H), 7.49(m, 5H, Ar-H), 7.56(tt, 1H, =CH), 7.73(s, 1H, NH). ^{13}C-NMR($CDCl_3$): δ= 14.5(q, 1C), 62.5(t, 1C), 116(d, 2C), 126.5(s, 1C), 127.5(d. 1C), 130(s, 1C), 133(d, 4C), 133.5(d, 3C), 135(s, 2C), 157(s, 1C), 166(s, 1C).

Ethyl-2-benzamido-3-(4-methoxyphenyl) acrylate (IV): IR (KBr)ν= 3223 cm^{-1}(PhNHC=O), 1717cm^{-1}(C=O), 1027-1240 cm^{-1}(C-O-C). ^{1}H-NMR ($CDCl_3$): δ = 1.34(t, 3H, CH_3), 3.8(s, 3H, O-CH_3), 4.31(q, 2H, CH_2), 6.8(dd, 2H, Ar-H), 7.48(m, 5H, Ar-H), 7.55(m, 1H, =CH), 7.71(s, 1H, NH), 7.89(d, 2H, Ar-H). ^{13}C-NMR($CDCl_3$) : δ= 15(q,1C) , 56(q , 1C) , 62(t , 1C) ,115(d , 2C) , 122(s , 1C) , 127(d , 2C) ,128(s ,1C) ,130(d , 2C) , 132(d , 2C) , 132.1(d , 2C) , 132.2(s , 1C) , 134(s , 1C) , 161(s , 1C), 166(s, 1C).

Ethyl-2-acetamido-3-phenylacrylate (V): IR (KBr) ν= 3252 cm-^{1}(CH_3NHC=O), 1750 cm^{-1}(C=O). ^{1}H-NMR ($CDCl_3$): δ = 1.35(t, 3H, CH_3), 2.14(s, 3H, CH_3), 4.31(q, 2H, CH_2), 7.26(m, 3H, Ar-H), 7.37(d, 2H, Ar-H), 7.46(s, 1H, NH). 7.37(d, 1H, =CH).^{13}C-NMR($CDCl_3$): δ = 15(q, 1C), 24(q, 1C), 63(t, 1C), 110(s, 1C), 115(d, 1C), 130.1(d, 2C), 131(d, 2C), 131(d, 1C), 134(s, 1C), 166(s, 1C), 169(s, 1C).

*Ethyl-2-acetamido-3-(4-chlorophenyl) acrylate (VI):*IR(KBr)ν = 3253cm^{-1}(CH_3NHC=O), 1714cm^{-1}(C=O). ^{1}H-NMR ($CDCl_3$): δ = 1.35(t, 3H, CH_3), 2.13(s, 3H, CH_3), 4.30(q, 2H, CH_2), 7.35(m, 5H,=CH + Ar-H), 7.70(m,

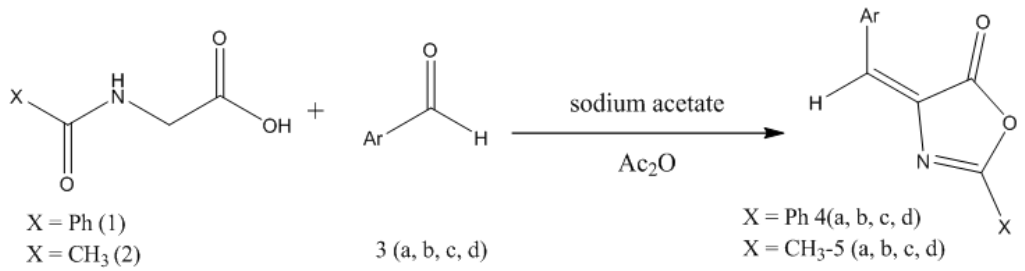
1H, NH).^{13}C-NMR($CDCl_3$): δ = 15(q, 1C), 24.9(q, 1C), 63(t, 1C), 125(s, 1C), 131.5 (d, 1C), 129.8(d, 2C), 132(d, 2C), 133(s, 1C), 136(s, 1C), 166(s, 1C), 169.5(s, 1C).

Ethyl-2-acetamido-3-(4-hydroxyphenyl) acrylate (VII): IR(KBr) ν= 3227 cm^{-1}(CH_3NHC=O), 1696 cm^{-1}(C=O). ^{1}H-NMR ($CDCl_3$): δ = 1.24(t, CH_3, 3H), 1.86(s, CH_3, 3H), 4.16(q, CH_2, 2H), 6.59(dt, 2H, Ar-H), 7.45(d, 2H, Ar-H), 6.16(m, 1H, =CH) , 9.3(s, 1H, NH), 9.68(s, 1H, OH). ^{13}C-NMR ($CDCl_3$): δ = 14(q, 1C), 22(q, 1C), 62(t, 1C), 116(d, 2C), 124(s, 1C), 126(d, 1C), 135.5(s, 1C), 132.5(d, 2C), 160(s, 1C), 166(s, 1C), 172(s, 1C).

*Ethyl-2-acetamido-3-(4-methoxyphenyl) acrylate (VIII):*IR(KBr)ν = 3264cm^{-1}(CH_3NHC=O), 1714cm^{-1}(C=O).^{1}H-NMR ($CDCl_3$): δ = 1.34(t, CH_3, 3H), 1.86(s, CH_3, 3H), 4.31(q, CH_2, 2H), 3.80(s, CH_3-O, 3H), 6.85(dt, 2H, Ar-H), 7.56(m, 1H, =CH), 7.71(s, 1H, NH), 7.89(d, 2H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ = 14.2(q, 1C), 23.4(q ,1C), 61.4(t, 1C), 55.8(q, 1C), 114.2(d, 2C), 121.7(s, 1C), 123.6(d, 1C), 126.6(s, 1C), 130.2(d, 2C), 159.8(s, 1C), 161.7(s, 1C), 170.4(s, 1C).

Discussion

Eight oxazolones (4 and 5 a, b, c, d)wereformed by the reaction of hippuric acid (1) andglycine" Aceturic acid" (2) with aldehydes such as benzaldehyde (3a), 4-chlorobenzaldehyde (3b), 4-hydroxybenzaldehyde (3c) and 4-methoxybenzaldehyde (3d) in basic medium (scheme 1) which were identified using IR, ^{1}H and ^{13}C NMRtechniquesand also by comparison with authentic samples prepared previouslyusing melting point and TLCas shown in table (1).



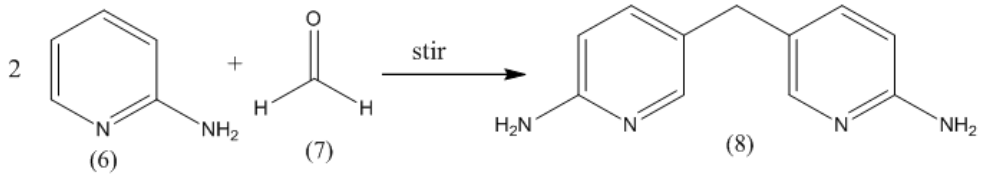
Scheme (1): Shows the preparation method of oxazolones

Table .1 The melting points, and % yields of synthesized compounds.

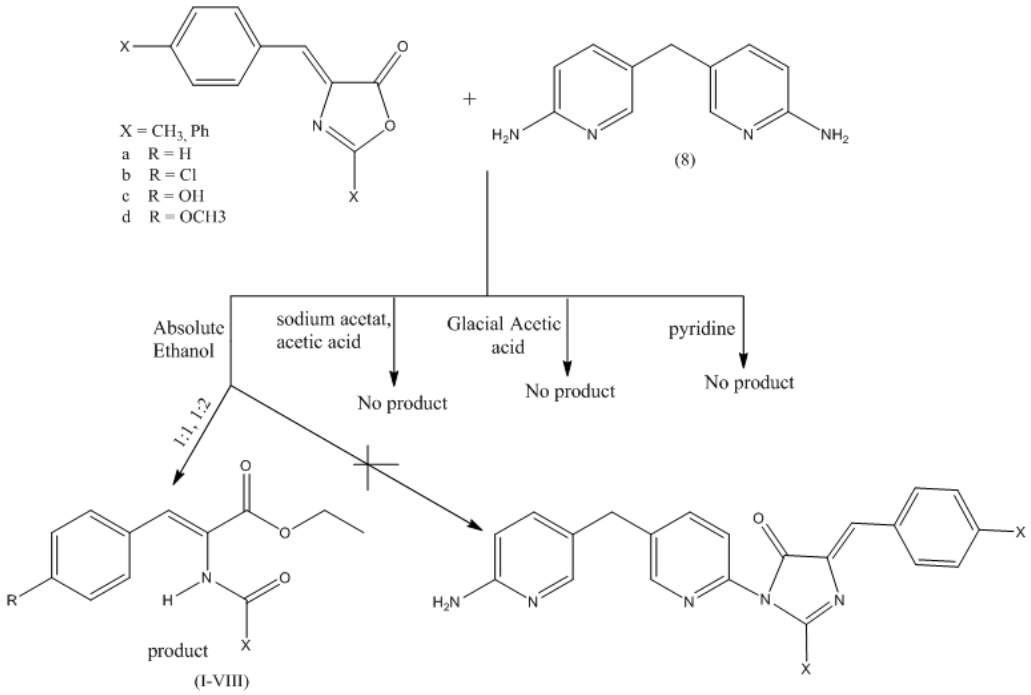
Compound no.	X	Ar.	Color	Yield (%)	m.p (°C)
4-a	ph	Phenyl	Yellow	68	164-165
4-b	ph	4-Chlorophenyl	Yellow	60	189-190
4-c	ph	4-Hydroxyphenyl	Yellow	64	180-182
4-d	ph	4-Methoxyphenyl	Yellow	61	158-159
5-a	CH_3	Phenyl	Yellow	27	150-152
5-b	CH_3	4-Chlorophenyl	Yellow	35	146-147
5-c	CH_3	4-Hydroxyphenyl	Yellow	38	138-140
5-d	CH_3	4-Methoxyphenyl	Yellow	36	109-110

The structure of4-arylidene-2-phenyl/methyloxazol-5(4H) one (4 and 5 a, b, c, d)characterized by the presence ofC=N and C=C stretching vibrations, which appeared at about 1650.95-1680 $cm^{-1}$and 1512.05-1562.25 cm^{-1},respectively.These special FTIR peaks indicated that oxazolone compounds were successfully formed.Moreover, The most important peak in the1H NMR spectrum of the oxazolone compounds(4 and 5 a, b, c, d)is singlet signal related to=CHwhich was observed at 7.92 ppm.Also, ^{13}C NMR spectra confirmed the presence of 16 carbon atom in the compound 4 a,b, and c and 17 carbon atom in compound 4d, whereas ^{13}C NMR technique also showed the total number of carbon atoms in compounds 5a,b, and c 11 and 12 carbon atomin compound 5d which indicates that the compounds(4 and 5 a, b, c, d)were prepared successfully.

The reaction between 2-aminopyridine with formaldehyde was carried out to produce 5,5'-methylenebis(2-aminopyridine) (8) asa white creamy color compound, it melted at 132-133°C,^{1}H and ^{13}C NMR confirmed the formation of the compound where the most significant signals appeared at 3.99 ppm,7.40 ppm,41.3 ppmand 158.1 ppm belonged to CH_2 and C-NH_2, respectively.



On the other hand,Because the study aimed to investigate the behavior of oxazolones towards nitrogen nucleophiles to afford the imidazolone, the reaction of oxazolones (4 and 5 a, b, c, d) with 5,5'-methylene bis(pyridine-2-amine) (8) was carried out by different ways.Although various procedureswere used where the reactants were refluxed utilizing sodium acetate with acetic acid, pyridine, and glacial acetic acid to prepare the required compound all methods were failed except one method was succeededwhen absolute ethanol was refluxed for 24 hour to give ester product instead of the target compound imidazolinone as shown in Scheme2. Besides, the same product was observed when repeating the experiment using a different ratio of reactants.



Scheme (2): Shows The different procedures and different mole ratio of reactants used in the synthesis

The formation of ethyl(Z)-2-acet / benz amido-3-phenylacrylate (I-VIII) can be explained by the nucleophilic attack of ethoxy ion instead of nitrogen atom in bis (pyridine -2-amine) on C-5 leading to ring opening and formation of the stable amide group. Infrared spectra of synthesized compounds have shown bands ranged from-1696 to1750 cm^{-1} and from 1632 to1659 cm^{-1}corresponding to C=O ester and amide, respectively. While bands for N-H amid appeared at about (3211-3264cm^{-1}).1H NMR analysis for compounds (I-VIII) showedsignals belonged to olefinic hydrogenappeared at about 7.40 ppm and amid group hydrogen N-H at 7.75 ppmwhich disappearedusing D_2O exchange technique.

The formation of the amide group proved the formation of the product because this group was not present in the reactants.

13C NMR also confirmed the successful preparation of the compounds (I-VIII), where the methylene carbon (CH_2,at 41.3 ppm) and amino carbon (C-NH_2, at 158.1 ppm)of compound (8)disappeared instead them (=CH) and carbonyl of amid group (HNCO) appeared at 128 and167.4 ppm,respectively.

IV. Conclusion

According to the literature, Oxazolones react with amines to giveimidazolone(El-Mekabaty2013). In this work more than two types of Oxazolones, 4-Arylidene-2-methyloxazol-5(4H)-one and 4-Arylidene-2-phenyloxazol-5(4H)-one were reacted with 5,5'-methylene bis(2-aminopyridine) using different techniques (EL-Makabaty et al.,2012), in the presence of Absolut ethanol, glacial acetic acid, pyridine, and sodium acetate with

acetic acid to prepare imidazolone (Suthakarana et al.,2008). instead of the desired imidazolone the acrylic esters were produced, eight novel acrylic esters (I-VIII) with different yields (5-86%) were prepared. This method is a new method for synthesis of acrylic ester. The synthesized compounds were characterized by IR, 1H NMR, 13C NMR,D_2O exchange, and APT spectroscopy.

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