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A Fast Synthesis of Unsaturated Azlactones Using Condensation Between Saturated Azlactones and Schiff Bases and Their Subsequent Aminolysis

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Abstract: Synthetic work related to penicillin has led to a considerable advance in the Chemistry of oxazoles and oxazolones. New general methods have been devised for constructing the ring, and much light has been thrown on the behaviour of functional groups attached to an oxazole nucleus. Most of the oxazolones previously described were of the type II, obtainable by the Erlenmeyer Synthesis from acylglycines and aldehydes from the action of acetic anhydride on α-acylamino acids. The acetic anhydride method of preparing oxazolones has remained the most general procedure. The objective of the present investigation was to develop a method for fast synthesis of unsaturated azlactones using condensation between saturated azlactones and Schiff bases and their subsequent aminolysis by using green chemistry technique which led to better yield and remarkable reaction rate enhancement with optimum utilization of energy.

The present investigation is carried out with three sequential objectives:

(a) Preparation of Schiff Bases
(b) Synthesis of 4- Arylmethylene-2-phenyl-2-oxazolin-5-ones (i.e. Unsaturated azlactones) and
(c) Aminolysis of 4- Arylmethylene-2-phenyl-2-oxazolin-5-ones in presence of glacial acetic acid.

2-Phenyl-2-oxazolin-5-one (**2**), i.e. saturated azlactone was generated by cyclizing hippuric acid (**1**) with *p*-toluenesulphonyl chloride (Tosyl Chloride) in the presence of triethylamine base in dry benzene at room temperature which declines the risk of high pressure development associated with solution phase reaction.

The resultant intermediate (**2)** which is saturated azlactone, was condensed with different aromatic imines (**3**) under mild conditions and subsequent removal of solvent under reduced pressure to get the targeted product 4-arylmethylene-2-phenyl-2-oxazolin-5-ones (**4**), i.e. unsaturated azlactones in appreciable yields with sufficient purity. If refluxing is continued by adding little glacial acetic acid in the same flask for further 10 minutes, the anilinolysis of the 1,5-bond of 4-arylmethylene-2-phenyl-2-oxazolin-5-ones (**4**), i.e. unsaturated azlactones, yielded the product N-phenyl-2-benzoylamino-3-arylpropenamides (**5**). It is noteworthy that the reaction is completed within maximum of 30 minutes and all the steps can be carried out in one flask.

Keywords: Schiff bases, Saturated Azlactones, Unsaturated azlactones, Z-isomer, Azlactonization, Atom Economy Route

I. INTRODUCTION

The classical Erlenmeyer azlactone synthesis has led to the synthesis of 5(4*H*)- oxazolones or Δ^2- oxazolin-5-one or Unsaturated Azlactones (III), are of the main topics of interest for the medicinal chemists as they show a number of pharmacological activities. Oxazolones can exist in different isomeric forms. Azlactones (oxazolones) may be regarded as cyclic esters of α-acylamino acids. They are broadly classified into two types, saturated azlactones (II) and unsaturated azlactones (III), as the two types show characteristic differences in properties.

2-Oxazolin-5-ones, also called 5-(4*H*)-Oxazolones, continue to attract the attention of chemists because of their usefulness as synthons and their diverse bio-potentiality. The subject has been reviewed[1-8] from time to time.

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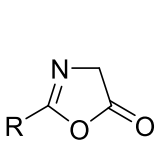
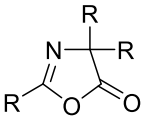
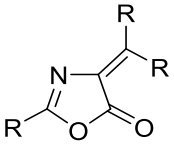


Δ^2- oxazolin-5-one
Or 5(4*H*)-oxazolone
Or Azlactone (I)



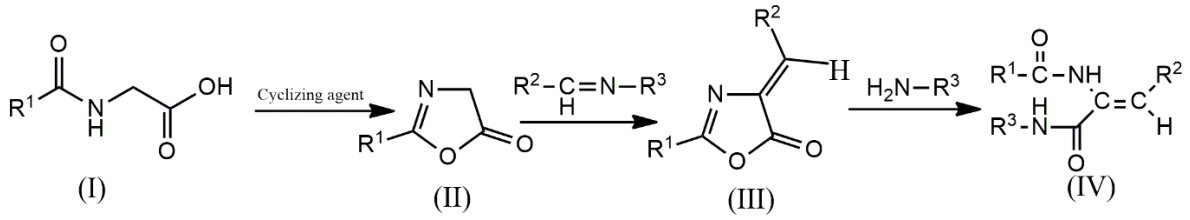
Saturated Azlactone (II)



Unsaturated Azlactone (III)

The synthesis of Oxazolone is a well-established process. 2-Oxazolin-5-ones (II), also called Saturated Azlactones, are usually synthesized by the cyclization of α-N-acyl amino acids (I) with the help of different cyclizing agents followed by the condensation with carbonyl compounds. It can also be synthesized by the cyclization of α-N-acylamino acids (I) with the help of different cyclizing agents followed by the condensation with Schiff bases (specially aromatic imines). 2-Substituted 4-arylmethylene-2-oxazolin-5-ones (III) are commonly known as Unsaturated Azlactones.

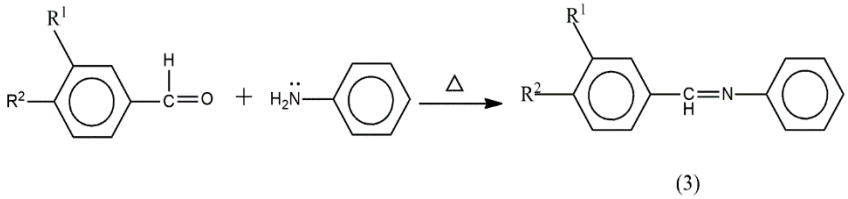
The reaction can further be proceeded in presence of glacial acid give substituted propenamides (IV). The classical Erlenmeyer azlactone synthesis[9] reported the formation of 4-Benzylidine-2-phenyl-2-oxazolin-5-one by the cyclization of hippuric acid with the aid of acetic anhydride and fused sodium acetate. The Erlenmeyer unsaturated azlactones have further been synthesized by using N,N-Dimethylchlorosulphitemethaniminium chloride[10], Phenyl isothiocyanate[11], Arylsulphonyl chloride[12], using microwaves on solid support[13,14], sonochemical reaction in ionic liquids[15] (*E*-isomers of azlactones are reported), mechanochemical approach[16] etc. In most of the cases, usually the stable geometric isomer with *Z*-configuration is obtained. Although the stable isomer of 4-Benzylidene-2-phenyl -2-oxazolin-5-one (III; R^1=Ph, R^2=Ph,) has been known for a long time.



(III) R^2= Aryl/ Alkyl; (*Z*)- isomer of azlactone.

(IV) R^1=Ph, R^2=Ph /substituted aryl, R^3=Ph; (*Z*)-isomer of propenamides.
Some dehydropeptides and N-substituted amides which may be obtained by aminolysis of azlactones have been reported to antitumor and CNS inhibiting properties. They are useful synthetic intermediates. The process aminolysis of azlactones is important because of its application in polymer chemistry.

SCHEME: 1



(3)

Figure-1: Preparation of Aromatic Schiff bases (Aromatic imines)

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SCHEME 2:

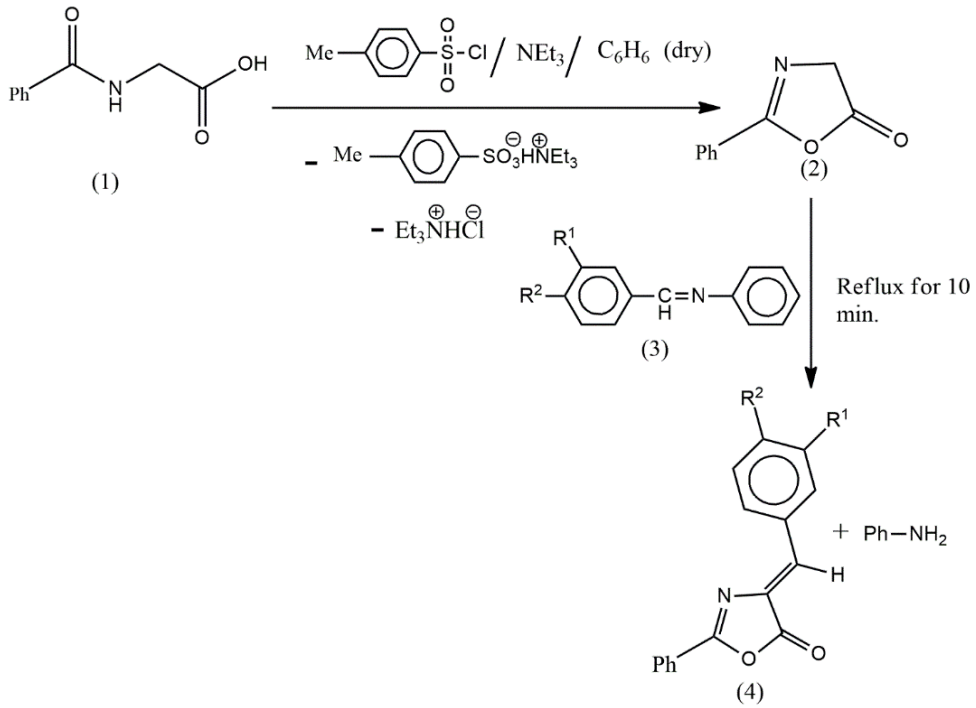

Figure-2: Synthesis of Unsaturated Azlactones (4) by the condensation between Saturated Azlactone (2) and Different Schiff bases (3).

SCHEME 3:

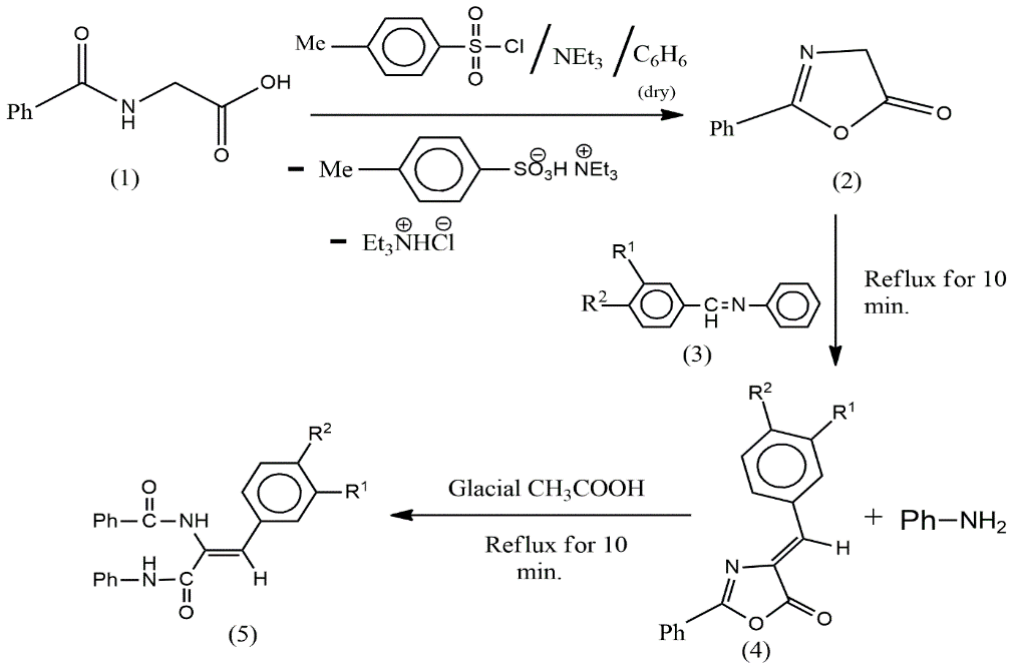

Figure-3: One flask synthesis of N-Phenyl -2-benzoylamino-3-Arylprop-2-enamides (5) using Atom Economy route.

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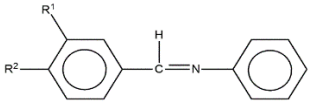
II. MATERIALS AND METHODS

All the prepared compounds are known in literature except **5d** and **5e**. The purity of the compounds was verified by TLC (silica gel based) and their melting points. Melting points were recorded by the Digital melting point apparatus and are uncorrected. The IR spectra of the compounds were recorded on IR Affinity-1, Shimadzu.

Scheme-1: Preparation of Schiff bases:



(3)

An equimolar mixture of an aldehyde and a primary amine was shaken for some time on water bath to give the desired imine. Products are washed with *n*-hexane and recrystallized with ethanol or aqueous ethanol.

Table-1: Physical data of Schiff bases (3) prepared

Schiff bases (3)	R^1	R^2	Yield* (%)	Recorded Melting point(°C)	Reported Melting point (°C)
3a	H	H	85%	51-52°C	53°C[21]
3b	$-NO_2$	H	92%	65°C	66°C[22]
3c	-OMe	-OH	90%	153°C	152-153°C[23]
3d	H	-OH	86%	196°C	196°C[21]
3e	H	-OMe	92%	66°C	65-67°C[24]

***** Yields are calculated based on the different aldehydes taken.

Where, 3a: Benzylideneaniline, 3b: *m*-Nitrobenzylideneaniline ;
3c: 4-Hydroxy-3-methoxybenzylideneaniline, 3d:4-Hydroxybenzylideneaniline,
3e: 4-Methoxybenzylideneaniline

Scheme-2: Preparation of 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones (4) using 2-oxazolin-5-one (2) and Schiff bases (3):

To a continuous stirred suspension of hippuric acid (**1**, 0.90 g; 0.005mol) in dry benzene (30mL/g of **1**) containing triethylamine (1.3mL; 0.0125mol), *p*-toluenesulphonyl chloride (0.95g; 0.005mol) was added and the mixture was shaken at room temperature until the acid crystals (**1**) dissolved and triethylamine salt separated out. The time required is 15- 20 minutes.Triethylamine salts were filtered off through suction and washed twice with dry benzene (3mL x 2). The washings and benzene solutions were combined. Then,the aromatic imine (**3**, 0.005mol) was added to the mixture which was heated under reflux for about 10 minutes and the content was concentrated to dryness under vacuum. The residue was triturated with 95% ethanol to afford the title compound i.e. 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones **(4)**. The solid material was isolated by suction, washed twice with cold ethanol and recrystalized from ethanol. The purity of the compounds is confirmed by their melting points. The purity of the compound was further verified by silica gel coated TLC plate in benzene eluent.

Table-2: Physical data of 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones (4).

4	R^1	R^2	Yield* (%)	Recorded Melting point (°C)	Reported Melting point (°C)
4a	H	H	60%	165-166°C	165-166°C[12]
4b	$-NO_2$	H	65%	174-176°C	175-176°C[12]
4c	-OMe	-OH	58%	157-158°C	157-158°C[12]
4d	-H	-OH	55%	172-174°C	172-173°C[18]
4e	-H	-OMe	70%	166-167°C	165-167°C[19]

* Yields are calculated based on Hippuric acid taken.

4a: 4-Phenylmethylene-2-phenyl-2-oxazolin-5-one

IR (KBr): ν_{max}= 1788 (C=O,oxazolone), 1770 (C=N), 1653 (4- C=C) cm^{-1}.

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4b: 4-(3-Nitrophenyl)methylene-2-phenyl-2-oxazolin-5-one
IR (KBr): ν_{max}= 1788(C=O,oxazolone), 1770 (C=N), 1653 (4- C=C) cm^{-1}.

4c: 4-(4-Hydroxy-3-methoxyphenyl) methylene-2-phenyl-2-oxazolin-5-one
IR (KBr): ν_{max}= 3483 (-OH), 1780(C=O,oxazolone), 1760 (C=N), 1636 (4- C=C) cm^{-1}.

4d: 4-(4-Hydroxyphenyl) methylene-2-phenyl-2-oxazolin-5-one
IR (KBr): ν_{max}= 3560 (-OH), 1793(C=O,oxazolone), 1654 (C=N), 1562 (4- C=C) cm^{-1}.

4e:4-(4-Methoxyphenyl) methylene-2-phenyl-2-oxazolin-5-one
IR (KBr): ν_{max}= 1790 (C=O,oxazolone), 1770 (C=N), 1650 (4- C=C) cm^{-1}.

Scheme-3: One flask Synthesis of N-phenyl-2-benzoylamino-3-arylprop-2-enamides (5) using Atom Economy route:

To a continuous stirred suspension of hippuric acid (**1**, 0.90 g; .0.005mol) in dry benzene (30 mL/g of **1**) containing triethylamine (1.3mL; 0.0125mol), *p*-tolulene sulphonyl chloride (0.95g; 0.005mol) was added and the mixture was shaken at room temperature until the acid crystals (**1**) dissolved and triethylamine salt separated out. The time required is 15-20 minutes. Triethylamine salts were filtered off through suction and washed twice with dry benzene (3mL x 2). The washings and benzene solutions were combined. The aromatic imines (**3**, 0.005mol) was added to the mixture which was then heated under reflux for about 10 minutes. The glacial acetic acid (4mL/g of **1**) was added and the reaction mixture was heated further under reflux for 5-10 minutes. On cooling, a solid separated out which was N-phenyl-2-benzoylamino-3-arylprop-2-enamides **(5).** The product was isolated by suction and washed with dry benzene. The products (**5**) were recrystallized from ethanol.

Table-3: Physical data of N-phenyl-2-benzoylamino-3-arylprop-2-enamides (5).

5	R^1	R^2	Yield*(%)	Recorded Melting point(℃)	Reported Melting point(℃)
5a	H	H	59%	234-235℃	233-235℃[25]
5b	$-NO_2$	H	63%	220-222℃	220-222℃[25]
5c	-OMe	-OH	55%	223-225℃	224-225℃[25]
5d	H	-OH	53%	190-192℃	Not found
5e	H	-OMe	69%	235-236℃	Not found

*Yields are calculated based on the Hippuric acid taken.

5a: 2-Benzoylamino-N-phenyl-3-phenylprop-2-enamide
IR (KBr): ν_{max}= 3300 (N-H, amide), 3260 (N-H, amide), 1640 (C=O, amide) cm^{-1}.

5b: 2-Benzoylamino-N-phenyl-3-(3-nitrophenyl)prop-2-enamide
IR (KBr): ν_{max}= 3245 (N-H, amide), 3260 (N-H, amide), 1660 (C=O), 1640 (C=C) cm^{-1}.

5c: 2-Benzoylamino-N-phenyl-3-(4-hydroxy-3-methoxyphenyl)prop-2-enamide
IR (KBr): ν_{max}= 3469 (-OH), 3211(N-H, amide), 3130(N-H, amide), 1647 (C=O, amide),1593(C=O, amide),1548(C=C) cm^{-1}.

5d: 2-Benzoylamino-N-phenyl-3-(4-hydroxyphenyl)prop-2-enamide
IR (KBr): ν_{max}= 3439(-OH), 3211(N-H, amide), 3122 (N-H, amide), 1656(C=O, amide), 1625(C=O, amide), 1575 (C=C) cm^{-1}.

5e: 2-Benzoylamino-N-phenyl-3-(4-methoxyphenyl)-prop-2-enamide
IR (KBr): ν_{max}= 3257 (N-H, amide), 3189 (N-H, amide), 1651(C=O, amide), 1602(C=O, amide), 1541(C=C) cm^{-1}.

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III. RESULTS AND DISCUSSIONS

With a view to converting the unstable 2-Phenyl-2-oxazolin-5-ones **(2)** obtained by *p*-toluenesulphonyl chloride mediated cyclization of α-N-benzoylglycine/ Hippuric acid **(1)** in dry benzene in the presence of triethylamine base at room temperature, into more stable 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones **(4)**, a suitable Schiff base **(3)** was added to reaction mixture, which was heated under reflux for about 10 minutes. The reaction proceeds with the condensation of arylidene group of Schiff base on the 4- position of 2-oxazolin-5-one (**2**) i.e. saturated azlactone along with the extrution of aniline ($PhNH_2$). 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones **(4)** obtained as the pure *(Z)*-isomer by the removal of solvent benzene under reduced pressure and further trituration with ethanol.

The product Unsaturated azlactone (**4)** can either be separated or the reaction may be extended further to get N-phenyl-2-benzoylamino-3-arylprop-2-enamide (**5**) without removing benzene using atom economy route and adding a little glacial acetic acid in the reaction mixture. The extuded aniline can act as nucleophile and can lead to the cleavage of the 1,5-bond of 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones **(4).** Therefore, the product N-phenyl-2-benzoylamino-3-arylprop-2-enamide (**5**) was also obtained from this 4-Arylmethylene-2-phenyl-2-oxazolin-5-one (**4**) which was not isolated but directly subjected to anilinolysis in presence of glacial acetic acid which bring about the cleavage of the 1,5-bond of unsaturated azlactone (**4**) by the attack of lone pair of electrons of N-atom of amines. Azlactones are thermolabile and isomerized to corresponding *(Z)*- isomer under present experimental conditions. It is noteworthy that the intermediate unsaturated azlactones (**4**) obtained by this method have *(Z)*- configuration, it is known that cleavage of the 1,5-bond in such compound does not change the stereochemistry of olefinic center at the C-4 position. Accordingly, the product N-phenyl-2-benzoylamino-3-arylprop-2-enamide (**5**) also possess (*Z*)-configuration.

In general, the IR spectra for 2-Oxazolin-5-ones i.e.Azlactones are obtained in the range of **1790- 1810 cm^{-1}**. IR (KBr): ν_{max}= 1790-1810 (C=O, oxazolone), 1770-1750 (C=N), 1650-1640 (4- C=C) cm^{-1}.

The IR spectra for N-Phenyl-2-benzoylamino-3-arylprop-2-enamides are obtained in the range of **1620-1640 cm^{-1}**. IR (KBr):ν_{max}= 3240-3400 (N-H, amide), **1620-1640 cm^{-1}** (C=O, amide), 1625-1650 (C=C) cm^{-1}.

IV. CONCLUSION

A fast and facile synthesis of unsaturated azlactones (**4**) using condensation between saturated azlactones (**2**) and Schiff bases (**3**) is carried out conveniently under milder conditions. It may be considered as one of the most milder Azlactonization method. The scheme is also extended for the synthesis of N-Phenyl -2-benzoylamino-3-arylprop-2-enamides (**5**) using the cleavage of 1,5-bond of **4** by extruded aniline using Atom Economy route under Green Chemistry methodology. The present procedure overcomes some of the disadvantages of the earlier methods[5,9] regarding speed of the reaction and stereochemical purity of the products.

For example, the Erlenmeyer azlactone synthesis[9] employs acetic anhydride for cyclization and it affords a mixture of *(E)*- and *(Z)*- isomers of the unsaturated azlactone (**4**) which have to be separated by fractional crystallization before using them for anilinolysis. This is rather time consuming and it lowers overall yield of amides (**5**). The crude (**4**) is subjected to aminolysis without isolation, so that reaction can be carried out in the same flask giving better yield of the final product with purity. The synthesised 4-Arylmethylene-2-phenyl-2-oxazolin-5-one **(4)** can be used as synthons for the development of different biopotential active molecules[20] and in the present investigation, it is alk-2-enamides (**5**). Further, the aryl moiety containing any free –OH group remains unaffected in our present synthesis.

It should be emphasized that the present procedure is simple and straight forward and all steps can be carried out in one flask. The solvent which is removed under reduced pressure can be reused which is good for environment. Considering the easy availability of the starting materials, the speed of the reaction, the milder experimental conditions, stereoche mical purity of the synthesized products, and the simplicity of the work-up, the present method appears to be potentially useful in Synthetic Organic Chemistry.

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