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Tosyl Chloride Mediated One Flask Facile Synthesis of 4-Arylmethylene-2-Phenyl-2-Oxazolin-5-Ones

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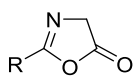
Abstract: The classical Erlenmeyer Azlactone Synthesis is one of the most common reaction to yield Azlactones or 5(4*H*)- Oxazolones or 2-Oxazolin-5-ones. The method involves cyclodehydration followed by condensation of different aromatic aldehydes with hippuric acid in the presence of acetic anhydride as a cyclising agent and anhydrous sodium acetate as a base in homogeneous phase. The method generally evolves a mixture of geometrical isomers of *E*- and *Z*-unsaturated azlactones. Azlactones are of the main topic of interest for the medicinal chemists as they show a number of pharmacological activities. Several procedures are developed time to time to produce varieties of unsaturated azlactones with methodological clarity and yield efficiency. In the present investigation, a disciplined route for the synthesis of *Z*-isomers of 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones are developed using Tosyl chloride (*p*-Toluene sulphonyl chloride) as cyclocondensing agent. The conversion of α-N-Benzoyl glycine i.e. Hippuric acid (1) to unstable 2-phenyl-2-oxazolin-5-one (2) i.e. saturated azlactone was carried out in dry benzene using tosyl chloride as cyclizing agent in the presence of triethylamine base at room temperature. Then the resultant 2-phenyl-2-oxazolin-5-one (2) is allowed to condense with arylaldehydes (3) by refluxing the content for 10 minutes. The insoluble triethylamine salts were filtered off under suction and washed twice with dry benzene. The filtrate and washings were combined and the solvent was removed under reduced pressure. On trituration of the residue with chilled ethanol, a yellow solid was obtained which was 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones (4) in very appreciable to good yield. All the required steps were carried out in one flask.

Keywords: Saturated azlactone, Unsaturated azlactone, *Z*-isomer, 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones**,** 4-(4-Methylphenyl) methylene-2-phenyl-2-oxazolin-5-one, 4-(4-Flurophenyl) methylene-2-phenyl-2-oxazolin-5-one, Disciplined route

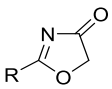
I. INTRODUCTION

Since classical Erlenmeyer azlactone synthesis in 1893, oxazolones are of the main topics of interest for the medicinal chemists as they show a number of pharmacological activities. Oxazolones can exist in five isomeric forms (I to V), all of which are known.



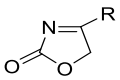
Δ^2- oxazolin-5-one

Δ^3-oxazolin-5-one



Δ^2- oxazolin-4-one

Δ^4-oxazolin-2-one

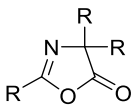


Δ^3-oxazolin-2-one

Or 5(4*H*)-oxazolone
Or Azlactone

(I) (II) (III) (IV) (V)

All these isomers, azlactones (oxazolones) may be regarded as cyclic esters of α-acylamino acids. They are classified into two types, saturated azlactones (VI) and unsaturated azlactones (VII), as the two types show characteristic differences in properties.



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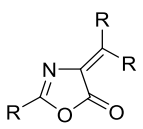

(VII)

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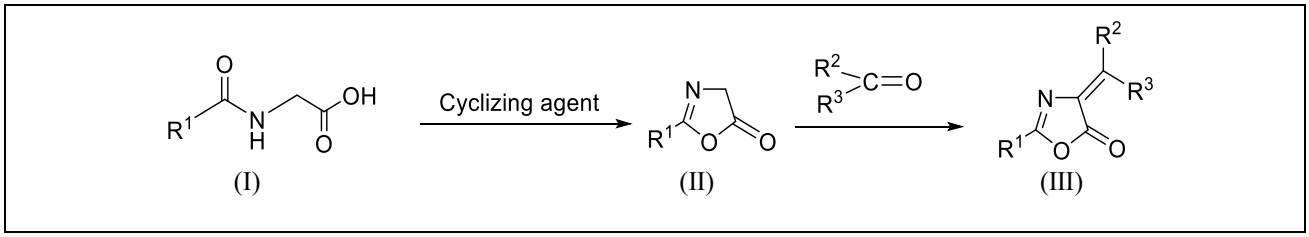
2-Oxazolin-5-ones, also called 5-(4*H*)-Oxazolones, continue to attract the attention of chemists because of their usefulness as synthons and their diverse bio-potentiality. The subject has been reviewed[1-8] from time to time.

2-Oxazolin-5-ones (III) are usually synthesized by the cyclization of α-N-acylamino acids (I) with the help of different cyclizing agents followed by the condensation with carbonyl compounds. 2-Substituted 4-arylmethylene-2-oxazolin-5-ones (III) are commonly known as unsaturated azlactones.

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, R^3=H) has been known for a long time.



(I) (II) (III)

(III) R^2= Aryl/ Alkyl and R^3= H; (*Z*)- isomer of azlactones

The objective of the present investigation was to develop a method for fast and facile synthesis of unsaturated azlactone by using green chemistry methodology which led to better yield and remarkable reaction rate enhancement with optimum utilization of energy.

2-Phenyl-2-oxazolin-5-one (**2**) was generated by cyclizing hippuric acid (**1**) with *p*-toluene sulphonyl 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**) was condensed with different aromatic aldehydes (**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**) in appreciable yields with sufficient purity. It is noteworthy that the reaction is completed within maximum of 30 minutes and all the steps are carried out in one flask.

SCHEME:

Table-1: Aromatic aldehydes with different substituents (R) used to synthesize 4-arylmethylene-2-phenyl-2-oxazolin-5-ones (**4**)

COMPOUND	R
4a	H
4b	3-NO_2
4c	4-NO_2
4d	4-Cl
4e	4-OH
4f	4-OMe
4g	4-Me
4h	4-F

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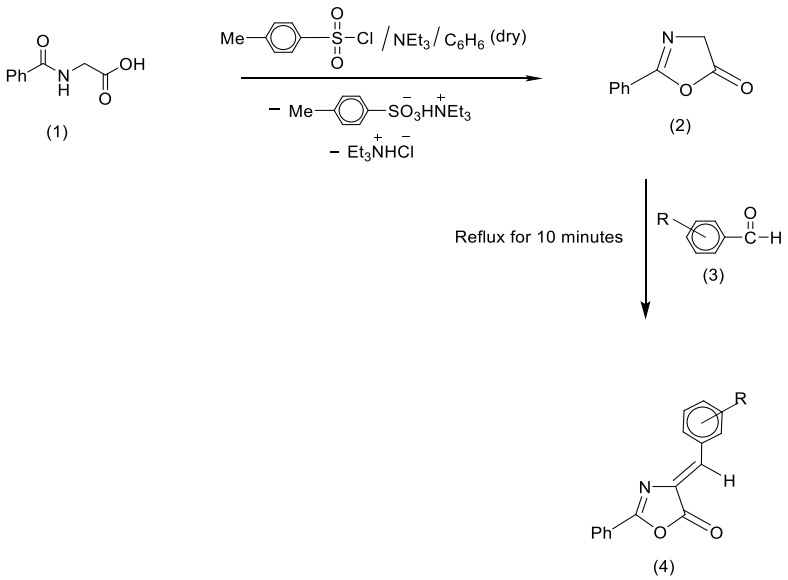

Figure-1: One flask Synthesis of 4-arylmethylene-2-phenyl-2-oxazolin-5-ones.

II. MATERIALS AND METHODS

All the prepared compounds are known in literature except **4g** and **4h**. The purity of the compounds was verified by TLC (silica gel based) and their melting points. Melting points were recorded by the metal block melting point apparatus and are uncorrected. The IR spectra of the compounds were recorded on IR Affinity-1, Shimadzu and Bruker, Alpha-II.

Preparation of 4- Arylmethylene-2-phenyl-2-oxazolin-5-ones (4): General Procedure

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. The aromatic aldehyde (**3**, Ar-CHO, 0.005mol) was added to the mixture which was heated under reflux for about 10 minutes.

Triethylamine salts were filtered off through suction and washed twice with dry benzene (3mL x 2). The washings and benzene solutions were combined and 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 are confirmed by their melting points.The purity of the compound was further verified by silica gel coated TLC plate in benzene eluent.

III. RESULT AND DISCUSSION

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 presence of triethylamine base at room temperature, into more stable 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones **(4)**, a suitable aromatic aldehyde **(3)** was added to reaction mixture which was heated under reflux for about 10 minutes. On work up, **4** was obtained as the pure *(Z)*-isomer. Azlactones are thermolabile and isomerized to corresponding *(Z)*- isomer under present experimental conditions.

The result is obviously due to the aldol type condensation of aldehydes at 4-methylene position of the saturated azlactone intermediate **(2)** with the elimination of water molecule.

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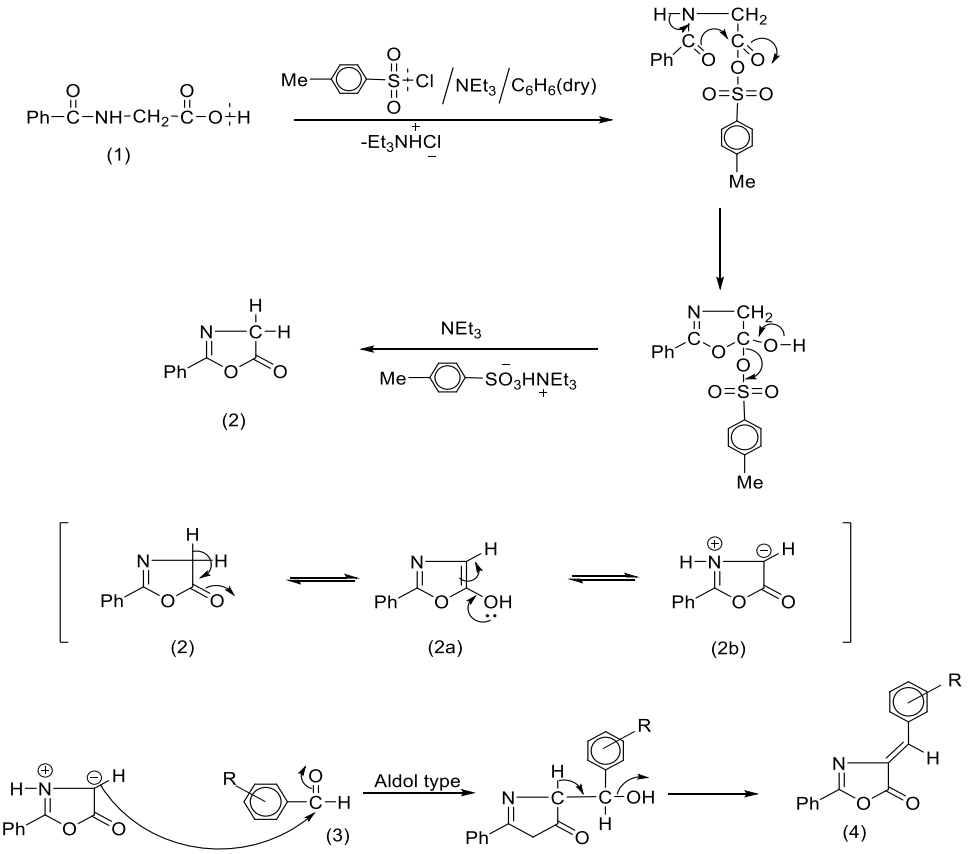

Figure-2: Proposed mechanism for cyclisation and condensation to synthesize 4-Arylmethylene-2-phenyl-2-oxazolin-5-ones **(4)**

In general, the IR spectra for 2-Oxazolin-5-ones 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}.

4a: 4-Phenylmethylene-2-phenyl-2-oxazolin-5-one
Yield=55%, m.p.:164-166^{O}C (Reported[12]:165-166^{O}C)

4b: 4-(3-Nitrophenyl) methylene-2-phenyl-2-oxazolin-5-one
Yield=60%, m.p.: 175-176^{O}C (Reported[12]: 175-176^{O}C)

4c: 4-(4-Nitrophenyl) methylene-2-phenyl-2-oxazolin-5-one
Yield=62%, m.p.:202-204^{O}C (Reported[17]: 198-200^{O}C)

4d: 4-(4-Chlorophenyl) methylene-2-phenyl-2-oxazolin-5-one
Yield=65%, m.p.:209-211^{O}C (Reported[17]: 209-211^{O}C)

4e: 4-(4-Hydroxyphenyl) methylene-2-phenyl-2-oxazolin-5-one
Yield=45%, m.p.:172-173^{O}C (Reported[18]: 172-173^{O}C)

4f: 4-(4-Methoxyphenyl) methylene-2-phenyl-2-oxazolin-5-one
Yield=70%, m.p.: 165-167^{O}C (Reported[19]: 165-167^{O}C)

4g: 4-(4-Methylphenyl) methylene-2-phenyl-2-oxazolin-5-one
Yield=55%, m.p.:146-148^{O}C (not found in the literature), IR=1794 (C=O, Oxazolone), 1697(C=N), 1652(C=C) cm^{-1}.

4h: 4-(4-Flurophenyl) methylene-2-phenyl-2-oxazolin-5-one
Yield= 65%,m.p.:184-186^{O}C (not found in the literature), IR=1795(C=O, Oxazolone), 1729(C=N), 1659(C=C) cm^{-1}.

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IV. CONCLUSION

Tosyl chloride is one of the most active cyclocondensing agent to produce 4-Arylmethylene-2-phenyl-2-oxazolin-5-one **(4)** using hippuric acid and arylaldehydes. 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**). Further 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].

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 used can be recycled and avoids the pollution impact to the environment. Considering the easy availability of the starting materials, the speed of the reaction, the milder experimental conditions, stereochemical 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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