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A Facile Synthesis of 4-(Heteroaryl) methylene-2-phenyl-2-oxazolin-5-ones and Their 1, 5-bond Cleavage Products

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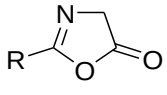
Abstract: The objective of the present investigation was to develop a method for a fast and facile synthesis of 4-(Heteroaryl)methylene-2-phenyl-2-oxazolin-5-ones (**4**) and their corresponding dehydroamino acids (**5**), their ethyl and methyl esters (**6**, **7**) and anilides (**8**) by solvolysis and aminolysis through 1,5-bond cleavage of 2-oxazolin- 5-ones (**4**) which are used as synthons.

An alternative modification for the fast and convenient synthesis of 4-(Heteroaryl)methylene-2-phenyl-2-oxazolin - 5-ones (**4**) where heteroaryl groups are furan (**4a**), pyrrole (**4b**) and thiophene (**4c**) moieties, is developed. They are the unsaturated azlactones. The conversion of α-N-benzoylglycine or hippuric acid (**1**) to unstable 2-phenyl-2- oxazolin-5-one (**2**) was carried out by using cyclising agents namely either Benzene sulphonyl chloride or *p*-Toluene sulphonyl chloride or Ethyl chloroformate in dry benzene in the presence of triethylamine as base at room temperature, which declined the risk of high temperature as well. After condensation of 2-Formyl heteroarenes namely 2-Formylfuran (**3a**), 2-Formylpyrrole (**3b**) and 2-Formylthiophene (**3c**) with 2-phenyl-2- oxazolin-5-one (**2**), the solvent was removed under reduced pressure. The removed solvent can be reused. These unsaturated azlactones i.e. 4-(Heteroaryl)methylene-2-phenyl-2-oxazolin-5-ones (**4**) can be isolated by trituration with chilled ethanol and can also be recrystallised with ethanol. Otherwise, the resultant unsaturated azlactones **4a**, **4b** and **4c** respectively were subjected to hydrolysis, ethanolysis, methanolysis (where ethanolysis and methanolysis are commonly called alcoholysis) and aminolysis directly in the same flask to obtain 2-Benzoyl amino-3-heteroarylprop-2-enoic acids (i.e. dehydroamino acids) (**5**), their esters namely Ethyl/ Methyl-2-Benzoylamino-3-heteroarylprop-2-enoates (**6**, **7**) and anilides namely N-Phenyl-2-Benzoylamino-3-heteroarylprop-2-enamides (**8**) respectively using the view of Green Chemistry methodology.

Keywords: 4-(Heteroaryl)methylene-2-phenyl-2-oxazolin-5-ones, Unsaturated azlactones, Synthons, Solvolysis, Anilinolysis, Green Chemistry.

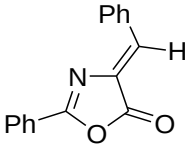
I. INTRODUCTION

The most well known route for the synthesis of azlactones involves the direct condensation of aromatic aldehydes and hippuric acid with a stoichiometric amount of fused sodium acetate as a base in the presence of acetic anhydride as the cyclodehydrating agent, which is known as the classical Erlenmeyer- Plochl reaction[11]. This reaction is popularly known as Erlenmeyer Azlactone Synthesis. The compound was 4-Benzylidene-2-phenyl-2-oxazolin-5-one (III) which was a 5-membered nitrogen containing cyclic ester and an azlactone name was coined accordingly. Azlactones are an important class of heterocyclic compounds because of their wide range of biological and bio-potential properties. Later, it has been found that the 2-oxazolin-5-ones obtained through acetic anhydride aided synthesis bearing certain drawbacks such as it may lead to the formation of a mixture of compounds with (*E*)- and (*Z*)- configurations (III and IV). Moreover, the free –OH group attached to the aryl moiety gets acetylated.



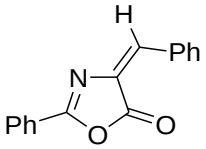
(I)

(II)



(III)

(*Z*)-Configuration



(IV)

(*E*)-Configuration

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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. The 1, 5-bond of 2-oxazolin-5-ones are very vulnerable and can be cleaved easily with the influence of suitable nucleophiles. Therefore, they can be used as synthons for the synthesis of wide variety of molecules.

4-(Heteroaryl) methylene-2-phenyl-2-oxazolin-5-ones (**4**) is one of the unsaturated azlactone where heteroaryl groups are furan, pyrrole and thiophene moieties. An attempt has been made to synthesized 4-(Heteroaryl) methylene-2-phenyl-2-oxazolin-5-ones (**4**) and its solvolysis and aminolysis products through an ecofriendly modified route in one flask.

Azlactones are important synthons for the synthesis of several biologically active compounds[1]. They are also useful precursors particularly for the synthesis of amino acids[2, 3], anilides[2 ,4] , peptides[5] , and their corresponding esters[3, 6]. Some dehydropeptides and N-substituted amides, which may be obtained by aminolysis of azlactones those have been reported to possess antitumor[7, 8, 9] and CNS inhibiting[10]properties.

N-Acyl-2,3-dehydroamino acids (2-acylamino-2-alkenoic acids, **5**), alkyl 2-acylamino-2-alkenoates (**6**,**7**) and N-substituted 2-acylamino-2-alkenamides (**8**) are in general prepared by hydrolysis, alcohololysis and aminolysis respectively of 2-substituted-4-alkylidene-2-oxazolin-5-one (**4**) which are in turn obtained by ERLENMEYER azlactone synthesis[11] or modification of this method[12-18].

SCHEME-1:

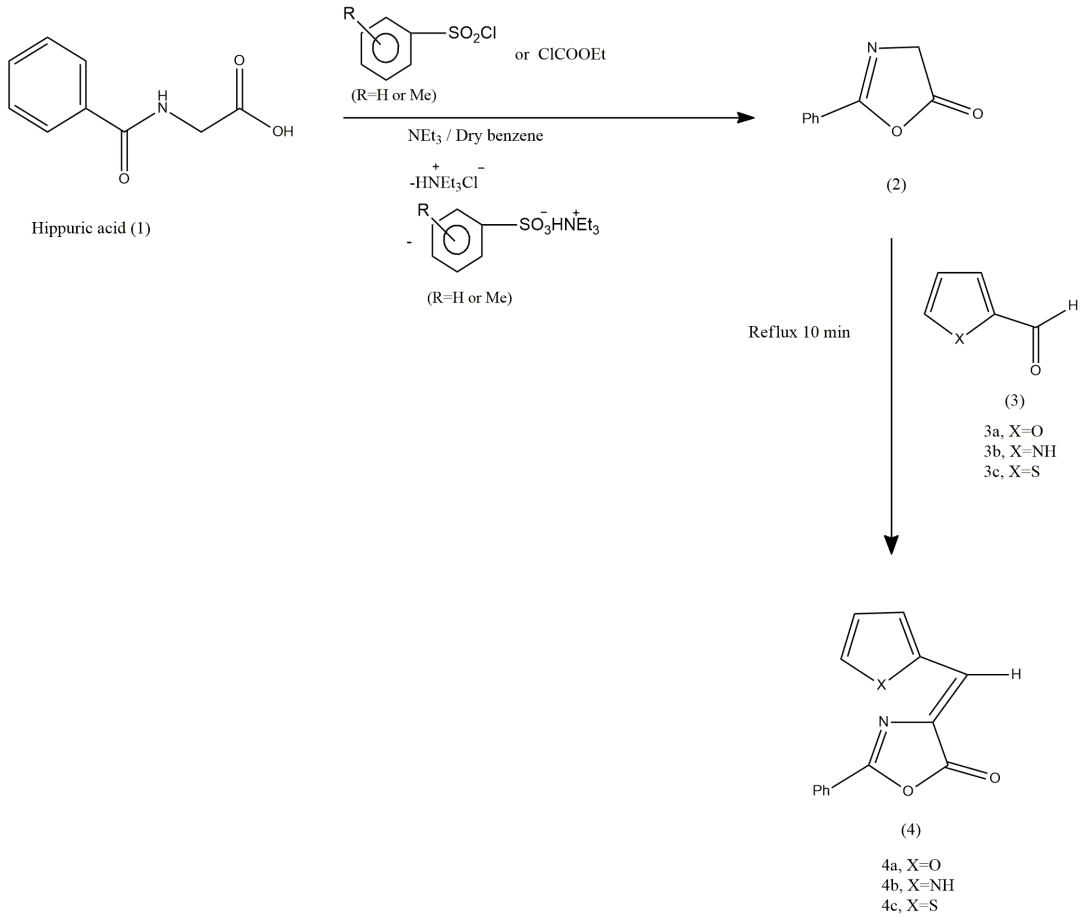

Figure-1: Synthesis of 4-(Heteroaryl)methylene-2-phenyl-2-oxazolin-5-ones (**4**)

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SCHEME-2

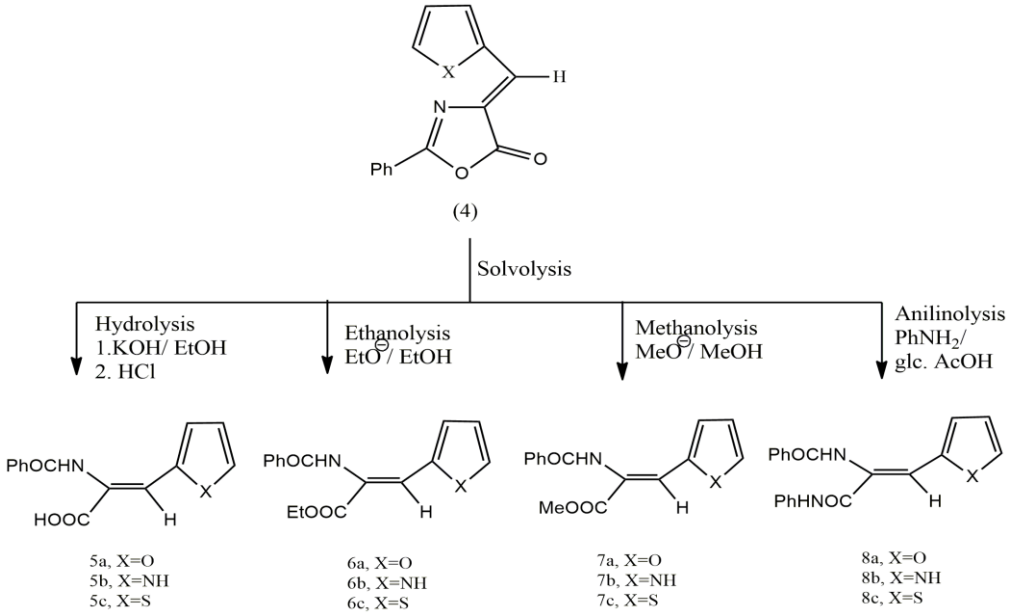

Figure- 2: Products synthesized by the cleavage of 1, 5-bond of 4-(Heteroaryl)methylene-2-phenyl-2-oxazolin-5-ones (**4**)

II. MATERIALS AND METHODS

Some of the prepared compounds are known in the literature[3, 12,19]. Some like **7a, 8a, 5c, 6c, 7c** and **8c** are not found in the literature. The purity of the compounds was verified by TLC (Silica gel plate/ Benzene), for anilides, benzene and ethyl acetate with the ratio of 9:1 are used. Melting points of the compounds were recorded by Digital melting point apparatus and are uncorrected. The IR spectra of the compounds were recorded on IR Affinity-1, Shimadzu Spectrophotometer.

4.1 Preparation of (*Z*)-4-((Furan-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4a)

4.1.1 Using benzene sulphonyl chloride as cyclizing agent:

To a stirred suspension of α-N-benzoylglycine (**1**, 1.0mole) in dry benzene (30mL/g of **1**) containing triethylamine (2.5mole), benzenesulphonyl chloride (1.0 mole) was added and the mixture was shaken at room temperature until the acid crystals dissolved and triethylamine salts separated out. The time required is 15- 20 minutes. The aromatic aldehyde (furfural, 1.0 mole) was added to the mixture which was then heated under reflux for about 10 minutes. Triethylamine salts were filtered off under suction and washed twice with dry benzene (5mL each). The benzene solution and washings were combined and concentrated to dryness under vacuum. The residue was triturated with 95% ethanol and the solid was filtered under suction to get the titled compound **4a**.

The compound was recrystallized with 95% ethanol, Yield: 50%, m.p. = 169-171ºC (Reported[12] m.p.= 170- 171ºC). The purity of the compound was further verified by silica gel coated TLC plate in benzene eluent. I.R.(KBr): ν[cm^{-1}]= 1800 (C=O,oxazolone), 1760 (C=N), 1650 (4 C=C).

4.1.2 Using *p*-Toluenesulphonyl chloride as cyclizing agent:

To a stirred suspension of α-N-benzoylglycine (**1**, 1.0mole) in dry benzene (30mL/g of **1**) containing triethylamine (2.5mole), *p*-Tolenesulphonyl chloride (1.0 mole) was added and the mixture was shaken at room temperature until the acid crystals dissolved and triethylamine salts separated out. The time required is 15- 20 minutes. The aromatic aldehyde (furfural, 1.0 mole) was added to the mixture which was then heated under reflux for about 10 minutes. Triethylamine salts were filtered off under suction and washed twice with dry benzene (5mL each). The benzene solution and washings were combined and concentrated to dryness under vacuum. The residue was triturated with 95% ethanol and the solid was filtered under suction to get the titled compound **4a**. The compound was recrystallized with 95% ethanol, Yield: 55%, m.p.= 169-171ºC (Reported[12] m.p.= 170- 171ºC). The purity of the compound was further verified by silica gel coated TLC plate in benzene eluent. I.R.(KBr): ν[cm^{-1}]= 1800 (C=O,oxazolone), 1760 (C=N), 1650 (4 C=C).

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4.1.3 Using Ethyl chloroformate as cyclizing agent:

To a stirred suspension of α-N-benzoylglycine (**1**, 1.0mole) in dry benzene (30mL/g of **1**) containing triethylamine (1.2 mole), Ethyl chloroformate(1.1mole) was added and the mixture was shaken at room temperature until the acid crystals dissolved and triethylamine salts separated out. The time required is 15- 20 minutes. The aromatic aldehyde (furfural, 1.0 mole) was added to the mixture which was then heated under reflux for about 10 minutes. Triethylamine salts were filtered off under suction and washed twice with dry benzene (5mL each). The benzene solution and washings were combined and concentrated to dryness under vacuum. The residue was triturated with 95% ethanol and the solid was filtered under suction to get the titled compound**4a**.

The compound is recrystallized by 95% ethanol, Yield: 48%, m.p.= 169-171ºC (Reported[12]m.p.= 170- 171ºC). The purity of the compound was further verified by silica gel coated TLC plate in benzene eluent. I.R.(KBr): ν[cm^{-1}]= 1800 (C=O, oxazolone), 1760 (C=N), 1650 (4 C=C).

4.2 Preparation of (*Z*)-4-((pyrrole-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4b):

4.2.1 Using benzenesulphonyl chloride as a cyclizing agent:

Same procedure was followed as method 4.1.1 but a tarry product was formed and the titled azlactone (**4b**) could not be isolated.

4.2.2 Using *p*-toluenesulphonyl chloride as a cyclizing agent:

Same procedure was followed as method 4.1.2 but a tarry product was formed and the titled azlactone could not be isolated.

4.2.3 Using Ethyl chloroformate as a cyclizing agent:

Same procedure was followed as method 4.1.3 but a tarry product was formed and the titled azlactone could not be isolated.

It should be noted that the title compound (*Z*)-4-((pyrrole-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (**4b**) is reported in the literature[20] which is prepared by using Acetic anhydride as cyclizing agent in presence of sodium acetate base.

4.3 Preparation of (*Z*)-2-phenyl-4-((thiophen-2-yl) methylene)-2-oxazolin-5-one (4c):

4.3.1 Using benzene sulphonyl chloride as cyclizing agent:

Same procedure was followed as method 4.1.1. to get the titled compound **4c**.

The compound was recrystallized with 95% ethanol, Yield: 60%, m.p. = 154-156ºC (Reported[19] m.p.= 156- 159ºC). The purity of the compound was further verified by silica gel coated TLC plate in benzene eluent. I.R.(KBr): ν[cm^{-1}]= 1790 (C=O, oxazolone), 1647 (C=N), 1616 (4, C=C), 1597 (C=C, Thiophene).

4.3.2 Using *p*-Toluenesulphonyl chloride as cyclizing agent:

Same procedure was followed as method 4.1.2 to get the titled compound **4c**.

The compound was recrystallized with 95% ethanol, Yield: 75%, m.p.= 154-156ºC (Reported[19] m.p.= 156- 159ºC). The purity of the compound was further verified by silica gel coated TLC plate in benzene eluent. I.R.(KBr): ν[cm^{-1}]= 1790 (C=O, oxazolone), 1647 (C=N), 1616 (4 C=C), 1597(C=C, thiophene).

4.3.3 Using Ethyl chloroformate as cyclizing agent:

Same procedure was followed as method 4.1.3 to get the titled compound **4c**.The compound is recrystallized by 95% ethanol, Yield: 58%, m.p.= 154-156ºC (Reported[19]m.p.= 156- 159ºC). The purity of the compound was further verified by silica gel coated TLC plate in benzene eluent. I.R.(KBr): ν[cm^{-1}]= 1790 (C=O, oxazolone), 1647 (C=N), 1616 (4 C=C), 1597(C=C, thiophene).

4.4 Solvolysis of unsaturated azlactones (4):

4.4.1 Preparation of 2-Benzoylamino-3-(furan-2-yl) prop-2-enoic acid (5a): Hydrolysis of (*Z*)-4-((Furan-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4a):

Method A:

To a stirred suspension of α-N-benzoylglycine (**1**, 1.0 mole) in dry benzene (30ml/g of **1**) containing triethylamine (2.5mole), *p*-toluenesulphonyl chloride (1.0mole) was added and the mixture was shaken at room temperature until the acid crystals dissolved and triethylamine salts separated out. The time required is 15- 20 minutes. The aromatic aldehyde (furfural, 1.0 mole) was added to the mixture which was then heated under reflux for about 10 minutes. Triethylamine salts were filtered off under suction and washed twice with dry benzene (5mL each). The benzene solution and washings were combined and evaporated to dryness under reduced pressure.

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To the above residue, obtained after removing benzene, KOH (1.2 mole) and 95% ethanol (80mL/g of KOH) were added and the mixture was shaken at room temperature until the potassium hydroxide pellets have completely dissolved. The mixture was then heated under reflux for about 15 min. The clear solution thus obtained was evaporated under reduced pressure. The residue was stirred with water (15mL/g of the acid) and this mixture was filtered under suction. The insoluble ester **6a**, can be purified by recrystallization from aqueous ethanol [yield: 10%, m.p. 125-127ºC]. Then the filtrate was chilled and was acidified with conc. HCl till complete precipitation. The precipitated acid was filtered and recrystallized from aqueous ethanol. Yield: 55%, m.p. : 209-210ºC (Reported[3]: 209-210ºC),I.R.(KBr): ν[cm^{-1}]=3300 (N-H),1700 (C=O, acid),1660 (C=O, amide),1650 (C=C),1610 (C=C, furan).

Method B:

4-(Furan-2-yl)methylene-2-phenyl-2-oxazolin-5-one(**4a,** 1.0mole) prepared by using Method 4.1 was taken in a round bottom flask, to this KOH (1.2 mole) and 95% ethanol (80ml/g of KOH)) were added and the mixture was shaken at room temperature until the potassium hydroxide pellets have completely dissolved. The mixture was then heated under reflux for about 15 min. The clear solution thus obtained was evaporated under reduced pressure. The residue was stirred with water (15mL/g of the acid) and this mixture was filtered under suction. The insoluble ester **6a**, can be purified by recrystallization from aqueous ethanol[Yield: 10-12%, m.p. 125-127ºC]. Then the filtrate was chilled and was acidified with conc. HCl till complete precipitation. The precipitated acid was filtered and recrystallized from aqueous ethanol. Yield: 85%, m.p.: 210-212ºC (Reported[3]: 209-210ºC),I.R.(KBr): ν[cm^{-1}]=3300 (N-H),1700 (C=O, acid),1660 (C=O, amide),1650 (C=C),1610 (C=C, furan).

4.4.2 Preparation of 2-Benzoylamino-3-(pyrrole-2-yl) prop-2-enoic acid (5b):
Hydrolysis of (*Z*)-4-(pyrrole-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4b):

The same procedure was carried out for hydrolysis as 4.4.1, where pyrrole-2-carboxaldehyde (3b) was used as an aromatic aldehyde. A tarry product is obtained and the expected titled compound (5b) could not be formed.

4.4.3 Preparation of 2-Benzoylamino-3-(thiophen-2-yl) prop-2-enoic acid (5c):
Hydrolysis of (Z)-4-((thiophen-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4c):
Method A:

The same procedure was carried out for hydrolysis as 4.4.1, Method A, where thiophene-2-carboxaldehyde (3c) was used as an aromatic aldehyde. The insoluble ester **6c**, can be purified by recrystallization from aqueous ethanol [Yield: 10%, m.p. 148-150ºC]. Then the filtrate was chilled and was acidified with conc. HCl till complete precipitation. The precipitated acid was filtered and recrystallized from aqueous ethanol. Yield: 55%,m.p.: 200-202ºC (Not reported),I.R.(KBr): ν[cm^{-1}]= 3269 (O-H), 3142 (N-H), 1691 (C=O, acid),1647 (C=O, amide),1602 (C=C),1556(C=C, thiophene).

Method B:

2-phenyl-4-((thiophen-2-yl)methylene)-2-oxazolin-5-one (**4c,** 1mole) prepared by using Method 4.3 was taken in a round bottom flask. The same procedure was carried out for hydrolysis as 4.4.1, Method B. The insoluble ester **6c**, can be purified by recrystallization from aqueous ethanol [Yield: 10%, m.p. 148-150ºC]. Then the filtrate was chilled and was acidified with conc. HCl till complete precipitation. The precipitated acid was filtered and recrystallized from aqueous ethanol. Yield: 95%, m.p.: 200-202ºC (Not reported), I.R.(KBr): ν[cm^{-1}]=3269 (O-H), 3142 (N-H), 1691 (C=O, acid),1647 (C=O, amide),1602 (C=C),1556 (C=C, thiophene).

4.4.4 Preparation of Ethyl- 2-benzoylamino-3-(furan-2-yl)prop-2-enoate (6a):
Ethanolysis of (*Z*)-4-(Furan-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4a)
Method A:

To a stirred suspension of α-N-benzoylglycine (**1**,1.0 mole) in dry benzene (30mL/g of **1**)) containing triethylamine (2.5mole), *p*-toluenesulphonyl chloride (1.0mole) was added and the mixture was shaken at room temperature until the acid crystals dissolved and triethylamine salts separated out. The time required is 15- 20 minutes. The aromatic aldehyde (furfural, 1.0 mole) was added to the mixture which was then heated under reflux for about 10 minutes. Triethylamine salts were filtered off under suction and washed twice with dry benzene (5mL each). The benzene solution and washings were combined and evaporated to dryness under reduced pressure. To the above residue, obtained after removing benzene, was treated with 95% ethanol (30mL/g of **1**) in the presence of a catalytic amount of KOH (1 pellet). The mixture was refluxed for about 15 to 20 min, and then concentrated to dryness under reduced pressure. The residue was triturated with cold water (15mL/g of **1**). The solid material was isolated by suction, washed twice with cold water, and recrystallized from ethanol. The product (**6a**) may also be recrystallized from benzene /petroleum ether (b.p. 40-60°C). Yield: 40%, m.p. : 126-128ºC (Reported[3]:125-127ºC),I.R.(KBr): ν[cm^{-1}]=3280(N-H),1715 (C=O, ester),1660(C=O, amide),1650 (C=C),1615(C=C, furan).

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Method B:

4-((Furan-2-yl)methylene)-2-phenyl-2-oxazolin-5-one (**4a,** 1mole) prepared by using Method 4.1was taken in a round bottom flask, to this KOH(1.2 mole) and 95% ethanol (80ml/g of KOH)) were added and the mixture was shaken at room temperature until the potassium hydroxide pellets have completely dissolved. The mixture was then heated under reflux for about 15 min. The clear solution thus obtained was evaporated under reduced pressure. The residue was triturated with cold water (15mL/g of **4a**). The solid material was isolated by suction, washed twice with cold water, and recrystallized from ethanol. The product (**6a**) may also be recrystallized from benzene /petroleum ether (b.p. 40-60°C). Yield: 80%, m.p. : 126-128°C (Reported[3]: 125-127°C),I.R.(KBr): ν[cm^{-1}]= 3280 (N-H), 1715 (C=O, ester), 1660 (C=O, amide), 1650 (C=C), 1615 (C=C, furan).

4.4.5 Preparation of Ethyl-2-benzoylamino-3-(pyrrole-2-yl) prop-2-enoate (6b):
Ethanolysisof (*Z*)-4-((pyrrole-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4b):

A tarry product is obtained and the expected titled compound (6b) could not be obtained by using method 4.4.4..

4.4.6 Preparation of Ethyl- 2-benzoylamino-3-(thiophen-2-yl)prop-2-enoate (6c):
Ethanolysis of (*Z*)-4-((thiophen-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4c):

Method A:

The same procedure is followed as given in 4.4.4. The product (**6c**) can either be recrystallized from ethanol or may also be recrystallized from benzene /petroleum ether (b.p. 40-60°C). Yield: 40%, m.p. : 187-188°C (Not reported), I.R.(KBr): ν[cm^{-1}]= 3250(N-H), 1710 (C=O, ester),1660 (C=O, amide),1600 (C=C),1577 (C=C, thiophene).

Method B:

2-Phenyl-4-((thiophen-2-yl)methylene)-2-oxazolin-5-one(**4c,** 1.0 mole) prepared by using method 4.3 was taken in a round bottom flask. The rest procedure is same as 4.4.4 to get the product **6c**. Yield: 90%, m.p. : 187-188°C (Not reported), I.R.(KBr): ν[cm^{-1}]= 3250(N-H), 1710 (C=O, ester),1660 (C=O, amide),1600 (C=C),1577 (C=C, thiophene).

4.4.7 Preparation of Methyl-2-benzoylamino-3-(furan-2-yl) prop-2-enoate (7a):
Methanolysis of (*Z*)-4-((furan-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4a):

Method A:

To a continuous stirred suspension of α-N-benzoylglycine (**1**, 1.0 mole) in dry benzene (30mL/g of **1**) containing triethylamine (2.5mol)), *p*-Tolenesulphonyl chloride (1.0 mole), 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 (furfural, 1.0 mole) 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 (5mL each). The washings and benzene solutions were combined and concentrated to dryness under vacuum. The residue was treated with 100% methanol (30 mL /g of **1**) in the presence of a catalytic amount of metallic sodium (0.07g, per g of **1**). The mixture was refluxed for 15-20 min, and then concentrated to dryness under reduced pressure. The residue was triturated with cold water (10-15mL/g of **1**). The solid material was isolated by suction, washed twice with cold water and recrystallised from methanol. The product (**7a**) may also be recrystillised from benzene / petroleum ether (b.p.40-60°C).Yield: 50%, m.p. : 179-180°C (Not Reported), I.R.(KBr): ν[cm^{-1}]=3215 (N-H), 1712 (C=O, ester),1651 (C=O, amide),1649 (C=C),1597(C=C, furan).

Method B:

4-((Furan-2-yl)methylene)- 2-phenyl-2-oxazolin-5-one(**4a,**1.0 mole) prepared via method 4.1 was taken in a round bottom flask, to this methanol (30 mL /g of **4a**) in the presence of a catalytic amount of metallic sodium (0.07g, per g of **4a**) was added. The mixture was refluxed for 15-20 min, and then concentrated to dryness under reduced pressure. The residue was triturated with cold water(10-15mL/g of **4a**). The solid material was isolated by suction, washed twice with cold water and recrystallized from methanol. The product (**7a**) may also be recrystallized from benzene / petroleum ether (b.p.40-60°C).Yield: 80%,m.p. : 179-180°C (Not Reported), I.R.(KBr): ν[cm^{-1}]= 3215 (N-H), 1712 (C=O, ester),1651 (C=O, amide),1649 (C=C),1597 (C=C, furan).

4.4.8 Preparation of Methyl-2-benzoylamino-3-(pyrrole-2-yl) prop-2-enoate (7b):
Methanolysis of (Z)-4-((pyrrole-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4b):

A tarry product is obtained and the expected titled compound (7b) could not be obtained by using procedure 4.4.7.

4.4.9 Preparation of Methyl-2-benzoylamino-3-(thiophen-2-yl) prop-2-enoate (7c):
Methanolysis of (Z)-4-((thiophen-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4c):

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Method A:
The same procedure was followed as 4.4.7 using 2-Formyl thiophene as an aromatic aldehyde. The product (**7c**) may be recrystillised either from ethanol or benzene / petroleum ether (b.p.40-60ºC).Yield: 60%,m.p. : 182-184ºC (Not Reported), I.R.(KBr): ν[cm^{-1}]=3253 (N-H), 1708 (C=O, ester),1651 (C=O, amide), 1631 (C=C), 1579 (C=C, thiophene).

Method B:
2-Phenyl-4-((thiophen-2-yl)methylene)-2-oxazolin-5-one (**4c**, 1.0mole) prepared via method 4.3 was taken in a round bottom flask. The rest procedure was same as 4.4.7. Yield: 90%, m.p. :182-184ºC (Not Reported), I.R.(KBr): ν[cm^{-1}] =3253 (N-H), 1708 (C=O, ester),1651 (C=O, amide), 1631 (C=C), 1579 (C=C, thiophene).

4.4.10 Preparation of N-phenyl-2-benzoylamino-3-((furan-2-yl) prop-2-enamide (8a):
Anilinolysis of (*Z*)-4-((furan-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4a):

Method A:
To a continuous stirred suspension of α-N-benzoylglycine (**1**, 1.0 mol) in dry benzene (30mL/g of **1**) containing triethylamine (1.2 mol), *p*-Tolenesulphonyl chloride (1.0 mole), 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(furfural, 1.0 mole) was added to the mixture which was heated under reflux for about 10 min. Triethylamine salts were filtered off through suction and washed twice with dry benzene (5mL each). The benzene solution and washing were combined and to the residue, the aniline (1.2 mole) and the glacial acetic acid (4 mL/g of **1**) were added and mixture was heated under reflux for 5-10 min. On cooling, a solid separated out which was isolated by suction and washed with benzene. The products (**8a**) were recrystallized from ethanol.Yield: 60%,m.p. : 201-203ºC (Not Reported).I.R.(KBr): ν[cm^{-1}]=3134 (N-H), 3105 (N-H),1654 (C=O, amide),1650 (C=C),1615 (C=C, furan).

Method B:
4-((Furan-2-yl)methylene)-2-phenyl-2-oxazolin-5-one(**4a**, 1.0mole) prepared via above mentioned cyclizing agents was taken in a round bottom flask, to this benzene (25mL/g of **4a**) ,then aniline (1.2 mole) and glacial acetic acid (4mL/g of **4a**) were added and the mixture was heated under reflux for 5-10 minutes. On cooling, a solid separated out which was isolated by suction and washed with benzene. The product (**8a**) was recrystallized from ethanol. Yield: 90%, m.p. : 201-203ºC (Not Reported).I.R.(KBr): ν[cm^{-1}]=3134 (N-H), 3105 (N-H),1654 (C=O, amide),1650 (C=C),1615 (C=C, furan).

4.4.11 Preparation ofN-phenyl-2-benzoylamino-3-((pyrrole-2-yl) prop-2-enamide (8b):
Anilinolysis of (Z)-4-((pyrrole-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (4b):
A tarry product is obtained and the expected titled compound (8b) could not be obtained by using the procedure 4.4.10.

4.4.12 Preparation ofN-phenyl-2-benzoylamino-3-((thiophen-2-yl) prop-2-enamide (8c):
Anilinolysis of (*Z*)-2-phenyl- 4-((thiophen-2-yl) methylene) -2-oxazolin-5-one (4c):

Method A:
The same procedure was followed as 4.4.10 by using 2-formyl thiophene as an aromatic aldehyde. The products (**8c**) were recrystallized from ethanol. Yield: 65%, m.p.: 216-218ºC (Not Reported).I.R.(KBr): ν[cm^{-1}]=3257(N-H), 3132 (N-H), 1651 (C=O, amide), 1622 (C=C),1598 (C=C, thiophene).

Method B:
2-Phenyl-4-((thiophen-2-yl)methylene)-2-oxazolin-5-one(**4c**, 1.0mole) prepared via above mentioned cyclizing agents was taken in a round bottom flask and the same procedure was followed as 4.4.10. The product (**8c**) was recrystallized from ethanol. Yield: 95%, m.p. :216-218ºC (Not Reported).I.R.(KBr): ν[cm^{-1}]=3257 (N-H), 3132 (N-H),1651 (C=O, amide), 1622 (C=C),1598 (C=C, thiophene).

III. RESULT AND DISCUSSION

The saturated azlactone **(2)** generated by cyclodehydration of α-N-benzoylglycine (**1**) with aryl sulphonyl chloride and triethylamine as base in benzene, is treated with an aromatic aldehydes (**3**) and heated under reflux for about 10 minutes. The crude product i.e. unsaturated azlactone **(4),** obtained by removing the solvent, is directly subjected to 1, 5-bond cleavage. The unsaturated azlactone (**4**) can also be isolated and may be recrystallized with ethanol. The purity

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of the compound **(4)** prepared by three different cyclizing agents namely benzenesulphonylchloride, *p*-toluenesulphonyl chloride and Ethyl chloroformate is verified by TLC (Silica gel Plate/benzene).The yield obtained from the reaction for **4** is highest in which *p*-Toluenesulphonyl chloride is used as a cyclizing agent. And hence further solvolysis and aminolysis reactions are carried out by using *p*-Toluenesulphonyl chloride. Hydrolysis is carried out by heating with ethanolic potassium hydroxide, followed by acidification with conc. HCl which affords the product 2-Benzoylamino-3-heteroarylprop-2-enoic acids **(5).** The result is obviously due to the generation of hydroxide ion as nucleophile which brings about the cleavage of the 1, 5-bond of unsaturated azlactones **(4)**. The ethyl ester **(6) is** obtained by treating the compound **4** with ethanol in presence of the catalytic amount of KOH (ethanolysis). It is due to the generation of ethoxide ion as nucleophile which cleaves the 1, 5-bond of the compound **4** with the formation of the product Ethyl 2-benzoylamino-3-heteroarylprop-2-enoates **(6).** The methyl ester **(7)** is obtained by treating the compound **4** with methanol in presence of the catalytic amount of metal sodium (methanolysis). It is due to the generation of methoxide ion as nucleophile which cleaves the 1, 5-bond of the compound **4** with the formation of the product Methyl 2-benzoylamino-3-heteroarylprop-2-enoates **(7).** For aminolysis, the compound **4** is heated with aniline in glacial acetic acid for about 10 min. On cooling the crystals of the product N-Phenyl-2-benzoylamino-3-heterarylprop-2-enamides **(8)** separates out. It follows the attack of lone pair of electrons on the N-atom of the aniline which leads to the cleavage of the 1, 5-bond of the compound **4**. The products recrystallized from ethanol and purity of the compounds are verified by TLC except the compound **(8)** due to its insufficient solubility in common solvents. The compounds are characterized by IR spectra and melting points.

The typical IR absorption bands for Unsaturated azlactone (**4**), carboxylic acid group **(5),** ester group **(6, 7),** and anilide **(8)** are observed at ≈ 1800, 1700, 1715 and 1660 cm^{-1} respectively.

It is noteworthy that the intermediate unsaturated azlactone obtained by this method have the (*Z*) -configuration, and it is known that cleavage of the 1, 5-bond in such compounds does not change the stereochemistry of the olefinic centre at C-4 position. Accordingly, the products obtained after solvolysis and aminolysis of **5**, **6**, 7 and **8**, all have *Z*-configuration. The present procedure does not have some of the drawbacks of the other methods. For example, Erlenmeyer azlactone synthesis[11, 20] employs acetic anhydride for cyclization and it affords a mixture of *E*- and *Z*–isomers of the unsaturated azlactones which have to be separated by fractional crystallizations before using them for hydrolysis, alcoholysis and aminolysis.

This is rather time consuming and it lowers the overall yield of compound acid (**5**), ester (**6, 7)** and anilide (**8**). Other methods involve the preparation of the acid, ester, anilide in several steps where as the generation of the unsaturated azlactone **(4)** by the present procedure is quite convenient; the crude product is subjected to hydrolysis, alcoholysis, or aminolysis without isolation, so that the reaction can be carried out in the same flask (Method A) and another flask after forming oxazolone (Method B) respectively**.** The steric integrity of the products is maintained at same time. Also the conversion of Hippuric acid (**1**) to unstable 2-phenyl-2-oxazolin-5-one (**2**) is carried out at the room temperature which declines the risk of high pressure development associated with solution phase reaction at high temperature. Moreover the solvent which is removed under reduced pressure can be reused which reduced the pollution impact.

It is worthwhile to mention that an attempt to synthesize (*Z*)-4-((pyrrole-2-yl) methylene)-2-phenyl-2-oxazolin-5-one (**4b**) by condensing 2-Phenyl-2-oxazolin-5-one (**2**) with 2-Formylpyrrole (**3**, X= NH) was failed by using the present cyclocondensing agents namely Benzenesulphonyl chloride, *p*- Toluene sulphonyl chloride and Ethyl chloroformate.

Consequently the hydrolysis, ethanolysis, methanolysis and aminolysis products also could not be prepared using the present methodologies.

IV. CONCLUSION

Considering the easy availability of the starting materials, the mild method of azlactonization, the speed of the reaction, the milder experimental conditions, the simplicity of the work-up, the present method for the rapid synthesis of 2-Phenyl-4-((furyl-2-yl)methylene)-2-oxazolin-5-one (**4a**) and 2-Phenyl-4-((thiophen-2-yl) methylene)-2-oxazolin-5-one (**4c**) and their solvolysis products (**5**,**6** and **7**) and aminolysis products (**8**) appears to be useful.

At the same time preparation of unsaturated azlactone with 2-Formylpyrrole and its solvolysis and aminolysis may not be suitable in the present investigation as these reactions produce a tarry product.

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