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Phenyl Isothiocyanate Mediated Facile Synthesis of 4-Arylidene-1-Phenyl-2-Substituted Styryl-2-Imidazolin-5-Ones and their Anti-Microbial Assessment

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Abstract: Phenyl isothiocyanate is a stable compound and can be used as a potential cyclizing agent. It is used as synthon due to their diverse reactions in synthetic organic chemistry. In comparison to isocyanates (-N=C=O), their sulphur analogues, isothiocyanates (-N=C=S) are less toxic and to some extent less hazardous. Though isocyanates are comparatively more reactive but the use of isocyanates is drastically limited by the researchers after December 3, 1984 which is the date of Bhopal disaster held in Union Carbide Factory, Bhopal, Madhya Pradesh (India) due to the leakage of Methyl isocyanate (MIC) where thousands of people were died due to the toxic exposure of MIC (Me-N=C=O)[18]. In the present investigation, a mixture of α-N-acetylglycine (1), phenyl isothiocyanate (2) and aromatic aldehydes (3) in a molar ratio of 1:1.2:2 respectively with pyridine as a catalyst was thoroughly mixed and was heated in oil bath for 30 minutes at 160°-170°C in an open vessel under solvent free condition. On work-up, the products obtained were 4-Arylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-ones (4). The reaction seems to proceed with the cyclization of α-N-Acetylglycine (1) by phenyl isothiocyanate (2) to produce 2-Methyl-2-oxazolin-5-one and arylideneimine (6) which condenses with methylene at 4-position of 2-Methyl-2-oxazolin-5-one and leads to the formation of 4-Arylidene -2-methyl-2-oxazolin-5ones (5) with the extrusion of aniline moiety. Another mole of aldehyde (3) condenses with aniline and forms second mole of arylideneimine which attacks at the active methyl group available at 2-position of oxazolones(5)forming 4-Arylidene-2-substituted styryl-2-oxazolin-5-ones(7). The subsequent anilinolysis of 1,5-bond of 4-Arylidene-2-substituted styryl-2-oxazolin-5-ones (7)and followed bycyclodehydration produces the targeted product 4-arylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-ones (4). These compounds were assessed in vitro for anti-microbial activity.

Keywords: Phenyl isothiocyanate, Synthon, α-N-acetylglycine, 4-Arylidene-1-phenyl-2-substituted styryl-2-imidazolin -5-ones, Anti-microbial activity

I. INTRODUCTION

The interest in chemistry of imidazolones has been attracting the chemists for a long time due to their usefulness as intermediates in natural products synthesis and common building blocks found in many biologically active molecules. They have a wide range of pharmacological profile which includes antiparkinsonian[1], anti-inflammatory [2,3], anticancer [4], anticonvulsant [5], antimicrobial [6,7] etc. These heterocyclic molecules have also very important impact in polymer chemistry [8,9].1-substituted-2-styryl-4-arylidene-2-imidazolin-5-ones were reported as the chromophore responsible for fluorescence of the green fluorescent protein of *Aquorea* and *Renilla* and their synthesis involved a tedious route [10]. In our present approach to construct a similar system in a ecofriendly and solvent free path. Here the route has been designed to synthesize 4-arylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-ones (4) using phenyl isothiocyanate (2) as a cyclocondensing agent.

The preparation of 4-Arylidene-1,2-diphenyl-2-imidazolin-5-ones by phenylisothiocyanatehave been reported in literature [11] . Aceturic acid or α-N-Acetylglycine(1) was heated withphenylisothiocyanate(2) in presence of different aromatic aldehydes (3) with their twice the amount as **1** using pyridine as catalyst under solvent free condition in an open vessel at 160°-170°C for about 30 minutes in dry media yielded 4-Arylidene-1-phenyl-2-substitutedstyryl-2-imidazolin-5-ones (4) in appreciable amount. Generally preparation of such type of complex organic molecule involves multistep synthesis. In present study, the synthesis of the targeted molecule was tried to carry out in one flask and in one step.

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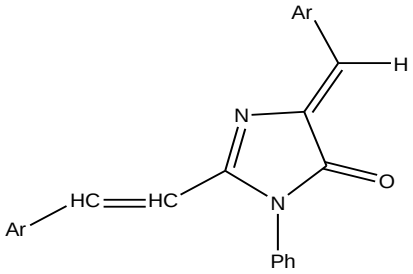

4

Compound 4	**Ar**
A	Ph
b	2-NO_2-C_6H_4
c	3-NO_2-C_6H_4
d	4-NO_2-C_6H_4
e	4-OH, 3-OMe, C_6H_3
f	4-Me_2N-C_6H_4

II. MATERIALS AND METHODS

The purity of compounds was verified by TLC (Silica gel/benzene) in case of compounds **4a, 4c** and **4e**, (Silica gel/benzene: ethyl acetate 9:1) in case of compound **4d**, (Silica gel/dichloromethane: *n*-hexane = 8.5:1.5) for **4f** and their melting points. The melting points were recorded by digital melting point apparatus and uncorrected. The IR spectra and NMR spectra of the compounds were recorded on IR Affinity-1, Shimadzu and JEOL ECS-400 Spectrophotometers respectively.

2.1 Synthesis of 4-Arylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-ones (4)

General procedure: A mixture of α-N-acetylglycine (1), phenyl isothiocyanate (2) and aromatic aldehydes (3) in a molar ratio of 1:1.2:2 respectively with pyridine as a catalyst was thoroughly mixed and was heated in oil bath for 30 minutes at 160°-170°C in an open vessel. The residue was washed with light petroleum (b.p. 40-60°C) to remove pyridine and then with saturated solution of $NaHCO_3$ to remove unreacted acid (1) if any. Then it was taken up in hot benzene , from which the benzene soluble part was separated from the benzene insoluble part. Thereafter benzene was removed under reduced pressure and the residue was triturated with chilled ethanol to get the title compound 4a and hot ethanol toget 4b, 4c, 4d. Acetone and chilled aqueous ethanol were used to triturate to get the solid 4f and 4e respectively. The compound 4f is highly soluble in ethanol so ethanol is not used to triturate it.

The typical IR absorption band for 2-imidazolin-5-ones ring is observed at ~1710cm^{-1}. Yield of the products are based on the amount of α-N-acetylglycine (1) used.(Figure- 1).

a) 4-Benzylidene-1-phenyl-2-styryl-2-imidazolin-5-one (4a). m.p. 238-240°C (Reported[12] 240-241°C). Yield: 57%. IR (KBr): 1707cm^{-1}(C=O imidazolone), 1630cm^{-1}(C=N), 1620cm^{-1}(C=C). ^{1}HNMR (DMSO-d_6): δ 6.6 (d, 1H, J=16 Hz, PhCH=C*H*), 7.3 (s, 1H, 4- C=C*H*), 7.4- 7.9 (m, 15H, Ar-*H*), 8.1 (d, 1H, J=16 Hz, PhC*H*=CH).

b) 2-(*o*-Nitrostyryl)-4-(*o*-nitrobenzylidene)-1-phenyl-2-imidazolin-5-one (4b). Yield: 45%, m.p. 209-210°C. ^{1}HNMR (DMSO-d_6): δ 6.6 (d, 1H, J=16 Hz, ArCH=C*H*), 7.3 (s, 1H, 4- C=C*H*), 7.4- 7.9 (m, 13H, Ar-*H*), 8.1 (d, 1H, J=16 Hz, ArC*H*=CH).

c) 2-(*m*-Nitrostyryl)-4-(*m*-nitrobenzylidene)-1-phenyl-2-imidazolin-5-one (4c). Yield: 66%, m.p. 231-233°C (Reported[13] 235°C) ^{1}HNMR (DMSO-d_6): δ 6.6 (d, 1H, J=16 Hz, ArCH=C*H*), 7.3 (s, 1H, 4- C=C*H*), 7.4- 7.9 (m, 13H, Ar-*H*), 8.1 (d, 1H, J=16 Hz, ArC*H*=CH).

d) 2-(*p*-Nitrostyryl)-4-(*p*-nitrobenzylidene)-1-phenyl-2-imidazolin-5-one (4d). Yield: 55%, m.p. 225-227°C. ^{1}HNMR (DMSO-d_6): δ 6.6 (d, 1H, J=16 Hz, PhCH=C*H*), 7.3 (s, 1H, 4- C=C*H*), 7.4- 7.9 (m, 13H, Ar-*H*), 8.1 (d, 1H, J=16 Hz, PhC*H*=CH).

e) 2-(*p*-Hydroxy-*m*-methoxystyryl)-4-(*p*-hydroxy-*m*-methoxybenzylidine)-1-phenyl-2-imidazoline-5-one (4e). Yield: 40%, m.p. 223-225°C.(reported[14] 225° C).IR(KBr): 3250 cm^{-1} and 3150 cm^{-1} (O-H), 1710 cm^{-1}(C=O imidazolone), 1660 cm^{-1} (C=N) and 1640 cm^{-1} (C=C). ^{1}HNMR (DMSO-d_6): δ 3.8 (s, 3H, OCH_3), 3.9(s, 3H, OCH_3), 6.3 (d, 1H, J=16 Hz, ArCH=C*H*), 6.75- 7.75 (m, 14H, 11x Ar-*H*, 4- C=C*H* and 2x Ar-O*H*), 7.9 (d, 1H, J= 16 Hz, ArC*H*=CH).

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f) 2-(*p*-N,N-Dimethylaminostyryl)-4-(*p*-N,N-dimethylaminobenzylidine)-1-phenyl-2-imidazolin-5-one (4f). IR(KBr): 1707(C=O imidazolone,), 1630(C=N) . 1600(C=C) cm^{-1} Yield: 36%, m.p. 185-187^{o}C. ^{1}HNMR (DMSO-d_6): δ 3.27 (s, 12H, 2x –N(CH_3)$_2$, 6.6 (d, 1H, J=16 Hz, PhCH=C*H*), 7.3 (s, 1H, 4- C=C*H*), 7.4- 7.9 (m, 15H, Ar-*H*), 8.1 (d, 1H, J=16 Hz, PhC*H*=CH).

2.2 Synthesis of 4-Benzylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-one from 4-Benzylidene-2-methyl-2-oxazolin-5-one and N-phenylbenzylideneimine

(*Z*)-4-Benzylidene-2-methyl-2-oxazolin-5-one (5, Ar= Ph)[15] and the Schiff base N-phenylbenzylideneimine (6, Ar= Ph)[16] were taken in equimolar proportions in glacial acetic acid (20mL/g of the oxazolone) containing freshly fused sodium acetate (0.48mol per 1mol of oxazolone and Schiff base) and the mixture was heated under reflux for about 4h in anhydrous condition. Then the solvent was removed under reduced pressure and the pasty mass was triturated with ethanol to give a solid which was filtered under suction and recrystallized from glacial acetic acid. Yield: 80%, m.p. 238-240^{o}C (Reported[17] 240-41^{o}C).

III. RESULT

A facile and rapid synthesis of 4-Arylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-ones (4) was carried out by the cyclocondensation reaction of aceturic acid or α-N-acetylglycine (1) with different aromatic aldehydes (3) in presence of phenyl isothiocyanate (2) as cyclizing agent and pyridine as catalyst in an open vessel by heating the mixture at 160-170^{o}C in an oil bath under solvent free condition. The reaction is completed within 30 minutes with much better yields 40-65%.

IV. DISCUSSION

The proposed route may be given as below (Figure-1):

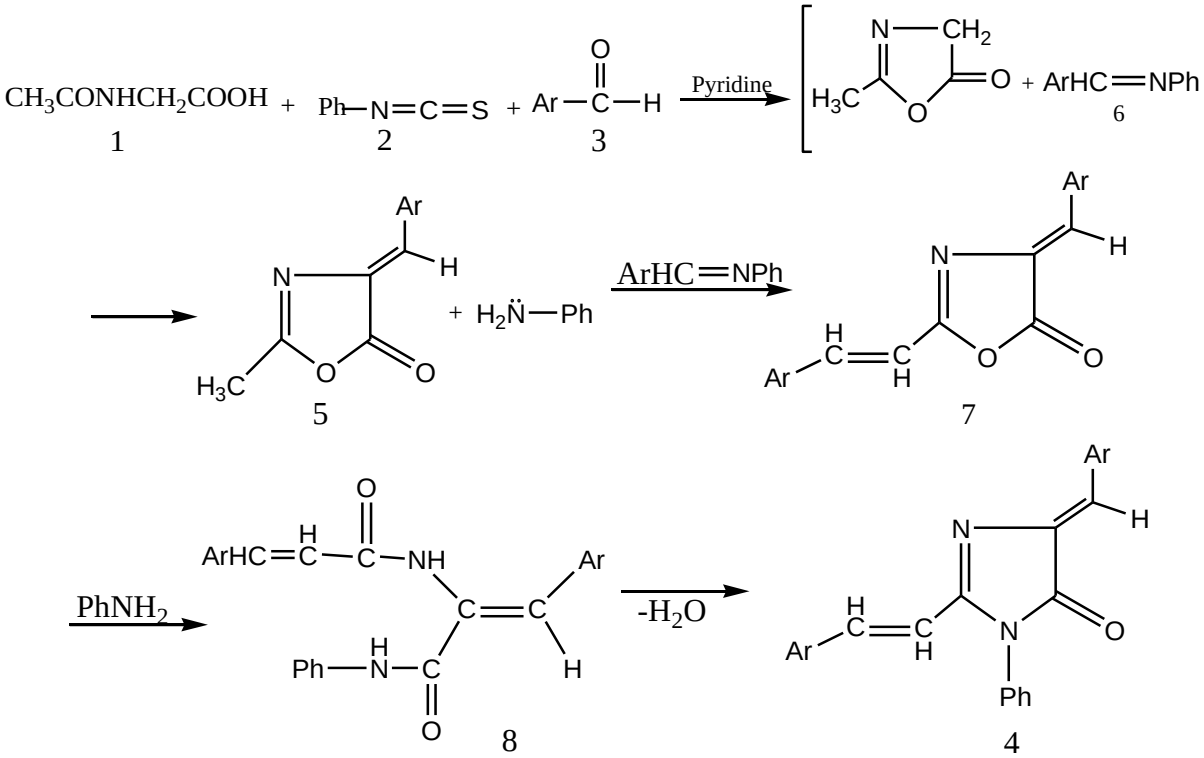

Figure-1: Synthesis of 4-arylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-ones

The reaction between α- N-Acetylglycine (1) and phenyl isothiocyanate (2**)** may produce 2-Methyl-2-oxazolin-5-one and arylideneimine (6) which condenses with methylene at 4-position of saturated azlactone and leads to the formation of 4-Arylidene -2-methyl-2-oxazolin-5ones (5) i.e. unsaturated azlactone with the extrusion of aniline moiety. Another mole of aldehyde (3) condenses with aniline and forms second mole of N-phenylarylideneimine. The second mole of N-phenylarylideneimine attacks at the active methyl group available at 2-position of oxazolones (5) which leads to the formation of 4-Arylidene-2-substituted styryl-2-oxazolin-5-ones (7). Further the subsequent anilinolysis of 1,5-bond of

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4-Arylidene-2-substituted styryl-2-oxazolin-5-ones (7) by available aniline leads to the formation of 8 which on cyclodehydration produces the targeted product 4-arylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-ones (4).

To establish the mechanism for the formation of the targeted product 4-arylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-ones (4), the interaction between 4-Benzylidene-2-methyl-2-oxazolin-5-one (5, Ar= Ph) with benzaldehydeanil (6, Ar= Ph) was studied to confirm the proposed route for the formation of the product 4 .

The starting material 4-Benzylidene-2-methyl-2-oxazolin-5-one (5)was prepared from the literature method[15]. The Benzaldehydeanil was prepared conveniently by mixing benzaldehyde and aniline with equimolar proportion and melting point was verified from literature[16]. The reaction between 4-Benzylidene-2-methyl-2-oxazolin-5-one (5,Ar= Ph) and Benzadehydeanil (6, Ar= Ph) was carried out in glacial acetic acid in presence of freshly fused sodium acetate strictly under anhydrous condition by refluxing the mixture for 4 hrs. The solvent was removed under reduced pressure and the resultant mass was triturated with ethanol. The product obtained was 4-arylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-ones (4). The TLC (silica gel/benzene) of the compounds 4a (prepared by using Phenylisothiocyanate) and 4 (prepared by using oxazolone and anil) show the same R_f value. which were further studied under IR spectroscopy to ensure the compound. The characteristic IR absorption band for 2-Imidazolin-5-one ring is observed at ~1710cm^{-1}.

V. ANTI-MICROBIAL ACTIVITY TEST

5.1 Sample Preparation: All the synthesized compounds **(4a-f)** were dissolved in mixture of DMSO and sterilized water (1:49) in 1mg/mL concentration.

5.2 Antibacterial test:

5.2.1 Pathogens used: In this analysis there are three types of pathogenic bacteria were used. *E coli* (8:2), *Pseudomonas* (8:2), and *Staphylococcus aureus* (8:2)
Media: Tomato juice agar
Standard reference: Streptomycin

5.2.2 Inoculation method: The inoculation was done by spread plate method. 150mL Of bacterial broth was pipetted out and spread homogeneously on media plates using an 'L' spreader. Then three filter paper discs of 0.5 cm diameter dipped in the prepared sample (5.1)and are placed in the plates at equidistance from each other. It is done for all compounds to all the three types of bacteria. The plates are incubated for about 24 hrs (incubation time) at 37±2^{o}C (incubation temperature). The compounds that are biologically active show inhibitory zones around the placed sample compounds.

5.2.3 Results of antibacterial test: All the prepared compounds were tested for antibacterial activity at 1mg/mL concentration for all the three above bacteria taking tomato juice agar media and using streptomycin as standard reference. Above all the compounds the 2-(*m*-methoxy, *p*-hydroxystyryl)-1-phenyl-4-(*m*-methoxy, *p*-hydroxybenzylidene)-2-imidazolin-5-one (i.e4e) is highest activity against the bacteria and the other five compounds did not show any fair kind of activity in our process of antibacterial test.

5.3 Antifungal test:

5.3.1 Pathogens used: In this test there are three types of fungi are used. *Fusariumoxysporum*, *F. chlamydosporum*, and *Absidia sp.*
Media: MRC media 8-Rojo Congo Agar
Standard reference: Amphotericin B

5.3.2 Preparation of the inoculum: The procedure followed here is called spore harvesting technique. 7 day old cultures grown in PDA slant are used for inoculation. 5mL of sterilized distilled water slant and hyphae were gently scraped out using a pre-sterilized disposable loop. The solution was vortexted for 1-2 minutes at a minimum speed. The solution is directly used for inoculation.

5.3.3 Inoculation method: 150mL of each organism solution is spread on 7 plates (6 plates for 6 test sample,1 for the reference sample) using 'L' spreader. Three filter paper discs of 0.5cm diameter was dipped in the prepared sample solutions were placed in each plates and incubated at 30±2^{o}C temperature at an inverted position. The results were recorded after 48hr.

5.3.4 Results of antifungal test: The all five compounds were also subjected to the antifungal analysis at 1mg/mL concentration taking MRC media 8- Rojo Congo Agar as media and Amphotericin B as standard reference. And the compounds here did not show any enhanced inhibitory effect in the process followed.

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VI. CONCLUSION

A fast and facile route was designed for the synthesis of some bioactive 4-arylidene-1-phenyl-2-substituted styryl-2-imidazolin-5-ones (4) . Considering the easy availability of the starting material, speed of the reaction, the milder experimental method under solvent free condition using green chemistry methodology and simplicity of the work-up, the present method seems to be potential for the synthesis of some bioactive 2-imidazolin-5-one derivatives.

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