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An ecofriendly Synthesis of Biologically active 4-Arylidene-2-phenyl-oxazolones at conventional method

[1]Santosh A. Jadhav, [2]Farooqui Mazahar, [3]Pardeshi Rajendra K.

[1]Department of Chemistry, Vivekanand Arts & S. D. Commerce and Science College Aurangabad (MS) 431001 India
[2]Department of Chemistry, Rafiq Zakaria College for Womens, Aurangabad- 431 001 India
[3]Department of Chemistry, S. R. College Ghansawangi, Dist. Jalna, affilated to Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (MS), 431 001 India.

E-mail (Corresponding Author):profsantoshjadhav@gmail.com

Abstract:

An ecofriendly synthesis series of **4-arylidene-2-phenyl-5(4*H*)-oxazolones or azlactones**(**3a-f**) catalyzed by Acetic anhydride and base catalyzed starting from easily available reactant molecules under reflux method. The reaction performed in combination of **water and ethanol** as green solvent under the simple conventional technique with good to excellent yields (90-96 %). The cyclisation followed by condensation of Hippuric acid **1** with various aldehydes**2** (**a-f)** catalyzed by sodium acetate and catalytic amount of acetic anhydride. The final products were characterized by ^{1}HNMR, Mass and compared there reported method.

Keywords: Hippuric acid, Aldehyde, Oxazolone or Azlactones, Water-ethanol, Conventional technique.

Introduction:

4-Arylidene-2-phenyl-5(4*H*)oxazolones, which are important intermediates of drug and or medicine from the several small molecules, such as amino acids[1-4], peptides[5, 6,] 2,2 di-subsituted- 2*H*-oxazol-5-ones with region and stereo control[7], precursors for other heterocyclic systems[8], Furthermore, oxazolones have been reported to exhibit a wide range of pharmaceutical properties[9], including anticancer [10], antitumor, antimicrobial[11], anti-inflammatory [12], antiviral [13] and anti-HIV [14] activities. These compounds can also be used as molecular photo switches[15] and optical sensors for the measurements of pH [16], for protein analysis by biosensor-coupling and photosensitive composition devices[17]. On these based importance to development of new methods for the facile and environmental benign synthesis of azlactones catalyzed by acetic anhydride Water-ethanol as green catalyst and solvent.

Previously, several methods have been reported for the synthesis of Oxazolone, for example, synthesis of a series of azlactones by the condensation of Hippuric acid with various aromatic

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aldehydes in the presence of acetic anhydride under ultrasonic irradiation conditions[18]. Azlactones may also be synthesized under solvent-free conditions with Nano silica-supported as tungstophosphoricacid[19] or using calcium acetate[20], aluminum oxide[21], and neutral alumina[22] under microwave irradiation conditions or organic inorganic hybrid polyoxometalates as a catalyst[23], ytterbium (III) triflate as a catalyst[24], Azlactones by Erlenmeyer method[25], which involves the condensation of aldehydes with Hippuric acid in the presence of sodium acetate and acetic anhydride and starting from hippuricacid[18-27]. All these synthetic methods have been used hazardous catalyst, solvent and cost effective method etc. It was envisaged that a green approach simple conventional method for the series of 4-arylidene-2-phenyl-5(4H)-oxazolones or azlactones in Water-ethanol mediated catalyze by sodium acetate and acetic anhydride from Hippuric acid and available various types aldehydes (Figure **1**).

Experimental Method:

Materials

The starting chemicals were purchased from Sigma Aldrich. All of the melting points were determined in open head capillary tubes a simple melting apparatus. These data have been presented as the uncorrected values. ^{1}H NMR spectra were measured on a Varian Gemini 300 MHz spectrometer. Chemical shifts (δ) have been expressed in ppm downfield from TMS, which was used as an internal standard. Mass spectra were recorded QUART-MASS JEOL-Accu TOF JMS-T 100LC Mass spectrometer 70 eV. All of the reactions were monitored by thin-layer chromatography (TLC) using aluminum TLC sheets coated with silica gel F254. TLC was also used to assess the purity of the synthesized.

General procedure for the preparation of azlactones 3a–f:

A mixture of hippuric acid (1.0 mmol), aromatic aldehyde (1.0 mmol), sodium acetate (0.5 mmol) was mixed in combination of Ethanol-water (2:1) in the presence of catalytic amount of acetic anhydride stirred for a few minutes and were reflux (**Table 1**). Upon completion of the reaction, as determined by TLC, the reaction mixture turned to a yellow solid, which was washed with cold water and recrystallized from ethanol to give the desired azlactones. The structures of the azlactones were confirmed based on a comparison of their melting point, HNMR and MS data with those from the literature.

Results and Discussion:

In continuation of our research work[28]. We synthesized, reported series of 4-arylidene-2-phenyl-5(4*H*)-oxazolones starting from the model reaction of Hippuric acid (1.0 mmol) **1**, aromatic aldehyde (1.0 mmol) **2 (a-f)**, sodium acetate (0.5 mmol) in solvent free and using solvent like methanol,ethanol, IPA, toluene, xylene, DCM, TCM, water, and combination of water-ethanol and catalytic amount of acetic anhydride at reflux condition (Table **1**). Herein, we observed good yield was obtained in combination of ethanol-water (2:1) (Table **1**, entry**11,12**). As we increases the quantity of ethanol in water as ethanol-water (2:1) then yield of the product were increases as yield 90-96 % (Table **1**, entry**13**) in less time of reaction compared to other optimizing of solvent (Table **1**). Thus, all the derivatives of 4-arylidene-2-phenyl-5(4*H*)-oxazolones / azlactones were synthesized in

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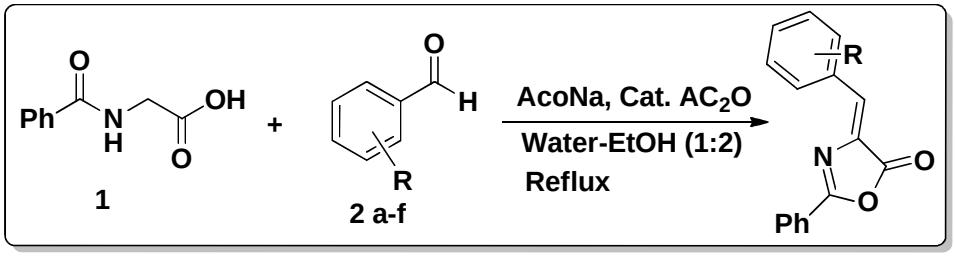
combination of ethanol-water (2:1) catalyzed by sodium acetate under simple conventionalmethod with better to excellent yields of the product 90-96 % (Table **2**). The unsubstituted and electron withdrawing group to aromatic aldehyde gave excellent yield (Table **2**, entry 1, 3-5) compared to other electron withdrawing and donating groups (Table **2**).

Reaction Scheme:



Reaction Scheme: Synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones or azlactones catalyzed by sodium acetate and acetic anhydride in water and ethanol as solvent.

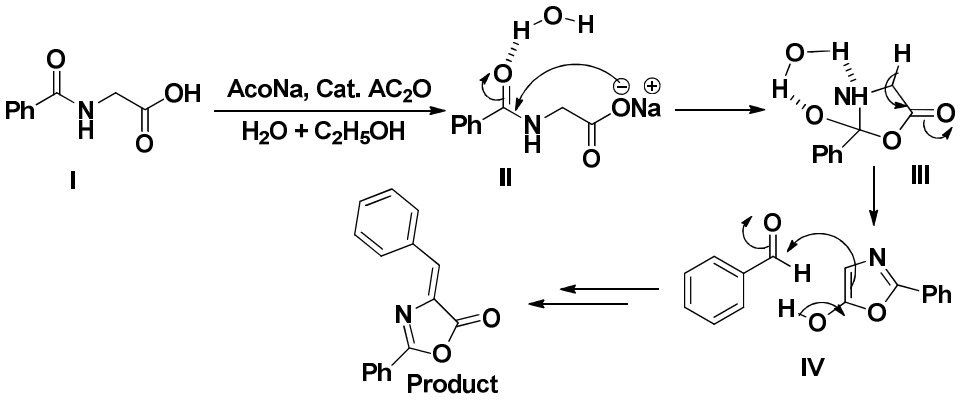


Figure 2. Plausible mechanistic path for the synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones or azlactones catalyzed by sodium acetate and acetic anhydride in water and ethanol as solvent.

Tables:

Table 1. Optimization of solvent for the synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones / azlactones.

Sr. no.	Solvent	Reaction condition	Time (hr)	Yield[a] (%)
1	Without	Reflux	3	00
2	Ethanol	Reflux	3	42

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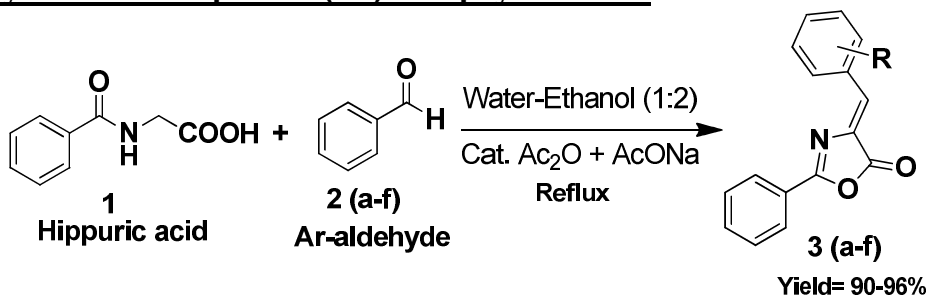
3	Methanol	Reflux	3	46
4	Iso.pr.alcohol	Reflux	3	36
5	Toluene	Reflux	3	32
6	Xylene	Reflux	3	36
7	DCM	Reflux	3	30
8	TCM	Reflux	3	36
9	Water	Reflux	3	50
10	PEG	Reflux	3	56
11	Ethanol-Water (1:1)	Reflux	3	62
12	Ethanol-Water (1:2)	Reflux	3	59
13	**Ethanol-Water (2:1)**	**Reflux**	**2,3**	**96,96**
14	Ethanol-Water (3:1)	Reflux	2	96

[a]**Reaction Condition:** hippuric acid (1.0 mmol), aromatic aldehyde (1.0 mmol), sodium acetate (0.5 mmol) was mixed in solvent in the presence of catalytic amount of acetic anhydride stirred and reflux.

Table 2. Synthesis of compound 3(a-f) with physical data:



Sr. no.	R	Reflux	Yield[b] (%)	Melting point (°C) Reported [Lit.]	Melting point (°C) Found
1	H	2	96	166-168[11]	171
2	4-Me	3	90	142-143[9,27]	141-142
3	4-NO_2	2	96	238-240 [9]	241
4	4-NO_2	2	95	203-205[4]	202
5	4-Cl	2	92	189-190 [9]	192
6	3,4,5-$(OMe)_3$	2	92	200-201[27]	199-201

[b]**Reaction Condition:** hippuric acid (1.0 mmol), aromatic aldehyde (1.0 mmol), sodium acetate (0.5 mmol) was mixed in combination of **Water-ethanol (1:2)** in the presence of catalytic amount of acetic anhydride stirred and reflux.

Characterization data of some synthesized products:

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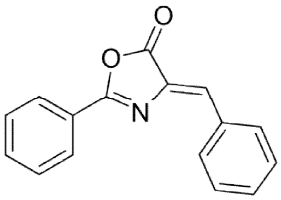
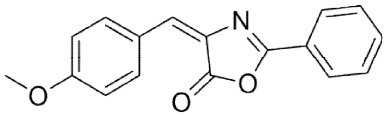
Spectral Characterization data 3a-f:

4-Benzylidene-2-phenyl-5(4*H*)-oxazolone (3a):



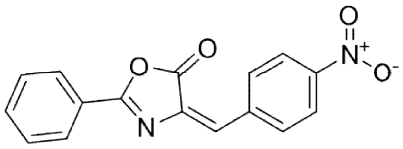
Mp. 171; IR (KBr): 1791, 1769 (C=O), 1654 (C=N), 1594 (C=C).; ^{1}H NMR (300 MHz, DMSO-d6): δ 7.35 (s, 1H, CH=C), 7.33–7.75 (m, 6H, Ar–H), 8.13 (d, 2H, J = 7.5 Hz), 8.30 (d, 2H, J = 7.8 Hz).; MS(ESI)m/z(%):249(M^+,100).

4-(4-Methoxybenzylidene)-2 phenyl-5(4H)-oxazolone (3b):



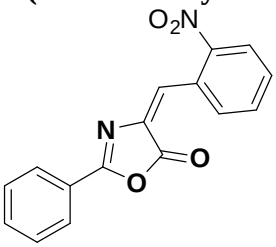
Mp. 141-142; IR (KBr): 1791, 1768 (C=O), 1655 (C=N), 1605 (C=C).; ^{1}H NMR (300 MHz, DMSO-d6): δ 3.88 (s, 3H, CH3), 7.11 (d, 2H, J = 9.0 Hz), 7.64 (d, 2H, J = 7.5 Hz), 7.69 (d, 1H, J = 6.9 Hz), 8.11 (d, 2H, J = 6.9 Hz), 8.30 (d, 2H, J = 9.0 Hz). For the E-isomer (71 %): 7.33 (s, 1H, CH=C), for the Z-isomer (29 %): 7.60 (s, 1H, CH=C).; MS (ESI) m/z (%): 279 (M^+, 88), 105 (100).

4-(4-Nitrobenzylidene)-2-phenyl-5(4H)-oxazolone (3c):



Mp. 241; IR (KBr): 1755, 1688 (C=O), 1625 (C=N), 1589 (C=C). ^{1}H NMR (300 MHz, DMSO-d6): δ 7.26–7.58 [m, 6H, (5Ar–H + 1CH=C), 7.74 (d, 2H, J = 7.5 Hz), 7.88 (d, 2H, J = 7.2 Hz).; MS (ESI) m/z (%): 294.15 (M^+, 0.5), 105 (100).

4-(2-Nitrobenzylidene)-2-phenyl-5(4H)-oxazolone (3d):



Mp. 202; IR (KBr): 1755, 1688 (C=O), 1625 (C=N), 1589 (C=C). ^{1}H NMR (300 MHz, DMSO-d6): δ 7.26–7.58 [m, 6H, (5Ar–H + 1CH=C), 7.74 (d, 2H, J = 7.5 Hz), 7.88 (d, 2H, J = 7.2 Hz).; MS (ESI) m/z (%): 294.15 (M^+, 0.5), 105 (100).

(Z)-4-(4-fluorobenzylidene)-2-phenyloxazol-5(4H)-one (4e):

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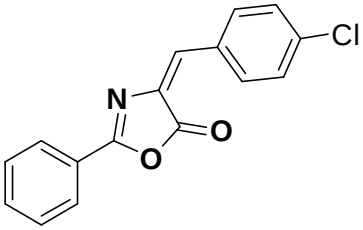
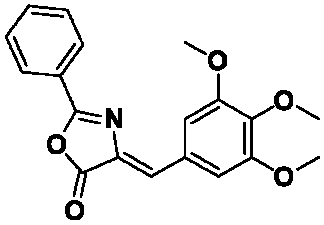


Mp.192˚C; IR (KBr)ν_{max}/cm^{-1}: 1508 (C=C-Ar), 1792 (C=O), 1653 (C=N), 2762 (ArC-H),1089 (Ar-Cl).; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.89(s, 1H, H-C=C), 7.18(d, 2H, Ar-H), 7.73(d, 2H, Ar-H), 7.53-7.90 (m, 5H, Ar-H).; MS (ESI):*m/z*(%) 268.07 [M+H].

6. (Z)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)oxazol-5(4H)-one (3f):



Mp.199-201˚C; IR (KBr)ν_{max}/cm^{-1}:1465(Ar-OMe), 1510 (C=C-Ar), 1792 (C=O), 1652 (C=N), 2763 (ArC-H).; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.38(s, 1H, H-C=C), 6.72(s,2H, Ar-H), 3.80(s, 9H, CH_3-O-Ar), 7.51-7.94(m, 5H, Ar-H).; MS (ESI):*m/z*(%) 340.34 [M+H].

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