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WATER-PEG MEDIATED ONE-POT SYNTHESIS OF 4-ARYLIDENE-2-PHENYL-5(4*H*)-OXAZOLONES OR AZLACTONES

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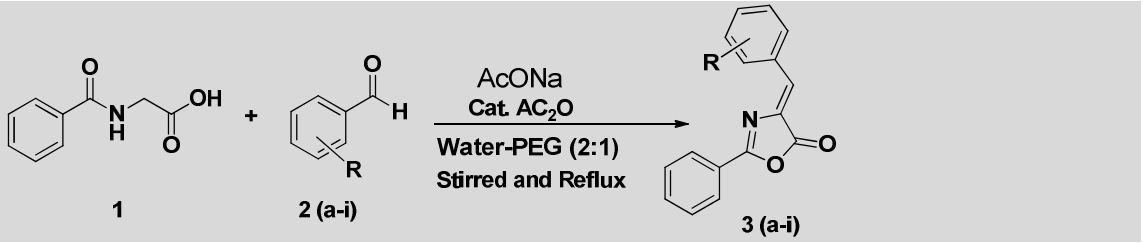
Abstract
Green approach one pot synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones or azlactone derivatives catalyzed by sodium acetate starting from easily available reactant molecules. The reaction performed in combination of water and polyethylene glycol (PEG-400) as green solvent under the simple conventional technique with good to excellent yields (90-98 %). The cyclisation followed by condensation of hippuric acid **1** and various types of aldehydes **2** (**a-i)** catalyzed by sodium acetate and catalytic amount of acetic anhydride. The final products were characterized by FTIR, ^{1}HNMR, Mass and compared there reported and found in good agreement.

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

Introduction

Nitrogen and oxygen containing five member heterocyclic compound such as 4-Arylidene-2-phenyl-5(4*H*)oxazolones, which are also known as azlactones, are important intermediates of drug and or medicine from the several small molecules, such as amino acids[i-iv], peptides[v, vi], 2,2 di-subsituted- 2H-oxazol-5-ones with region and stereo control[vii], precursors for other heterocyclic systems.[viii] Furthermore, oxazolones have been reported to exhibit a wide range of pharmaceutical properties [ix], including anticancer [x], antitumor, antimicrobial[xi], anti-inflammatory [xii], antiviral [xiii] and anti-HIV [xiv] activities. These compounds can also be



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

used as molecular photo switches[xv] and optical sensors for the measurements of pH [xvi], as well as biosensor-coupling and photosensitive composition devices for protein analysis.[xvii] Based on these importance, the development of new methods for the facile and environmental friendly synthesis of azlactonescatalyzed by sodium bi-carbonateand PEG-Water as green catalyst and solvent.

In past, several methods have been reported for the synthesis of azlactones / oxazolone, for example, synthesis of a series of azlactones by the condensation of hippuric acid with various aromatic aldehydes in the presence of acetic anhydride under ultrasonic irradiation conditions.[xviii] Azlactones may also be synthesized under solvent- free conditions using Nano silica-supported tungstophosphoricacid[xix] or using calcium acetate[xx], aluminum oxide[xxi], and neutral alumina[xxii] under microwave irradiation conditions or organic inorganic hybrid polyoxometalates as a catalyst[xxiii], ytterbium (III) triflate as a catalyst[xxiv], under solvent free condition. By the important route for the synthesis of Azlactones-Erlenmeyer method[xxv], which involves the condensation of aldehydes with hippuric acid in the presence of sodium acetate and acetic anhydride and starting from hippuric acid.[xviii-xxv]All these synthetic methods have been used hazardous catalyst, solvent and cost effective method etc. In earlier our research works for the synthesis of some heterocycles in combination of water-PEG as green solvent.[xxvi]It was envisaged that a totally green approach one-pot, one-stage method for the series of 4-arylidene-2-phenyl-5(4H)-oxazolones or azlactones in PEG-Water mediatedcatalyze by sodium acetate and acetic anhydridedirectly from hippuric acid and available various types aldehyde (Figure **1**).

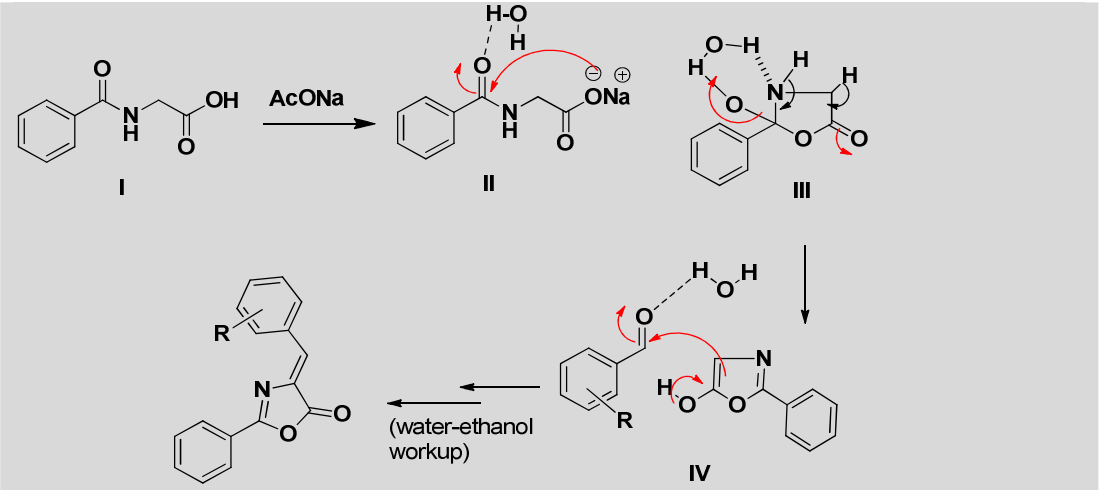


Figure2. Plausible mechanistic path for the synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones or azlactones catalyzed by sodium acetate and acetic anhydride.

Results and discussion

We report, reported series of 4-arylidene-2-phenyl-5(4*H*)-oxazolones / azlactones staring from the model reaction of hippuric acid (1.0 mmol)**1**, aromatic aldehyde (1.0 mmol)**2 a-i**, sodium acetate(0.5 mmol) in solvent free and solvent like methanol, ethanol, IPA, toluene, xylene, DCM, TCM, water, PEG-400 and combination of water-PEGand catalytic amount of acetic anhydride at 80° C to reflux condition (Table **1**).Herein, we observed good yield was obtained in combination of Water-PEG-400 (1:1) (Table **1**, entry **11**). As we increases the quantity of water in PEG-400 as Water-PEG-400 (2:1) then yield of the product were

increases as an excellent yield 98 % (Table **1**, entry **14**) in less time of reaction compared to other optimizing of solvent (Table **1**). If we increase the quantity of water in PEG-400 at reflux condition and 80-90°C temperature the yield of product were decreases even after increases the time of reaction (Table **1**, entry **15-19**).

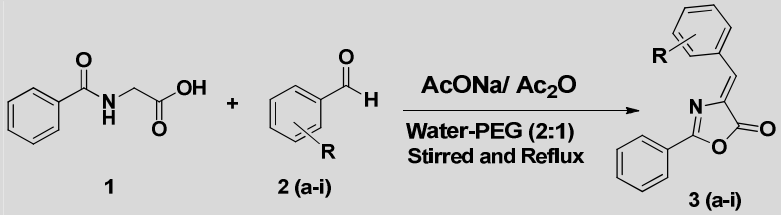
Thus, all the derivatives of 4-arylidene-2-phenyl-5(4*H*)-oxazolones / azlactones were synthesized in combination of Water-PEG-400 (2:1) catalyzed by sodium acetateat reflux condition with better to excellent yields of the product 90-96 % (Table **2**). The unsubstituted and electron withdrawing group (-NO_2) to aromatic aldehyde gave excellent yield (Table **2**,entry 1, 5) compared to other electron withdrawing and donating groups (Table **2**).

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

Sr. no.	Solvent	Temperature (°C)	Time (hr)	Yield[a] (%)
1	Without	Reflux	3	00
2	Ethanol	Reflux	3	42
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	2.5	50
10	PEG	Reflux	2.5	56
11	Water-PEG (1:1)	Reflux	2.5	62
12	Water-PEG (1:2)	Reflux	2.5	49
13	Water-PEG (1:4)	Reflux	2.5	38
14	**Water-PEG (2:1)**	**Reflux**	**2**	**98**
15	Water-PEG (3:1)	Reflux	2.5	83
16	Water-PEG (2:3)	Reflux	2.5	53
17	Water-PEG (2:4)	Reflux	2.5	49
18	Water-PEG (2:1)	90	3	62
19	Water-PEG (2:1)	80	3	58

[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 were reflux.

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



Sr. no.	R	Time (hr)	Yield[b] (%)	Melting point (°C) Reported [Lit.]	Melting point (°C) Found
1	H	2	98	166-168[21]	170
2	4-OMe	2	96	155-156[09]	157
3	4-Cl	2	96	189-190[09]	191
4	4-NMe_2	2	90	205-206[09]	205
5	4-NO_2	2	98	238-240[09]	240
6	2-Cl	2	96	150-152[09]	153
7	2-Br	2	93	144-145[08]	145
8	3,4-$(OMe)_2$	2	92	148-150[21]	152
9	4-CH=CH-	2.5	90	130-131[21]	130

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

Experimental Method:

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. IR spectra were recorded as KBr disks on a PerkinElmer RXIFTIR spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini 300 MHz spectrometer (Palo Alto, CA, USA). Chemical shifts (δ) have been expressed in ppm downfield from TMS, which was used as an internal standard. H NMR spectra were recorded in DMSO-d6 and the coupling constants (J) reported in Hz. 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 (Merck, Darmstadt, Germany).

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

A mixture of hippuric acid (1.0 mmol), aromatic aldehyde (1.0 mmol), sodium acetate (0.5 mmol) was mixed in combination of Water-PEG (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 azlactone. The structures of the azlactones were confirmed based on a comparison of their melting point, IR, NMR and MS data with those from the literature.

Spectral Characterization data 3a-i :

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

Mp. 170; IR (KBr): 1792, 1768 (C=O), 1653 (C=N), 1592 (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. 157; IR (KBr): 1789, 1768 (C=O), 1653 (C=N), 1602 (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-Chlorobenzylidene)-2-phenyl-5(4H)-oxazolone (3c):

Mp. 191; IR (KBr): 1796, 1768 (C=O), 1652 (C=N), 1586 (C=C).;^{1}H NMR (300 MHz, DMSO-d6): δ 7.50 (d, 1H, J = 7.5 Hz), 7.61 (d, 1H, J = 8.7 Hz), 7.66 (d, 1H, J = 7.5 Hz), 7.73 (d, 1H, J = 7.5 Hz), 7.94 (d, 1H, J = 7.5 Hz), 8.14 (d, 2H, J = 7.5 Hz), 8.33 (d, 2H, J = 8.7 Hz).; For the E-isomer (86 %): 7.37 (s, 1H, CH=C), for the Z-isomer (14 %): 7.47 (s, 1H, CH=C). MS (ESI) m/z (%): 285 (M^{++} 2, 30), 283 (M^+, 90), 105 (100).

4-(4-(Di-methylamino) benzylidene)-2-phenyl-5(4H)-oxazolone (3d):

Mp. 205; IR (KBr): 1758, 1762 (C=O), 1648 (C=N), 1606, 1582 (C=C).; ^{1}H NMR (300 MHz, DMSO-d6): δ 3.07 (s, 6H, 2CH3), 6.83 (d, 2H, J = 9.0 Hz), 7.33 (s, 1H, CH=C), 7.58–7.66 (m, 3H), 8.06 (d, 2H, J = 6.6 Hz), 8.17 (d, 2H, J = 8.7 Hz).; MS (ESI): m/z (%): 292 (M^+, 91), 105 (100).

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

Mp. 240; IR (KBr): 1753, 1689 (C=O), 1622 (C=N), 1586 (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-Chlorobenzylidene)-2-phenyl-5(4H) oxazolone (3f):

Mp. 153; IR (KBr): 1794, 1772 (C=O), 1687, 1652 (C=N), 1601 (C=C).;^{1}H NMR (300 MHz, DMSO-d6): δ 7.46 (s, 1H, CH=C), 7.50 (d, 2H, J = 7.8 Hz), 7.57–7.67 (m, 3H), 7.94 (d, 2H, J = 7.2 Hz), 8.15 (d, 1H, J = 6.9 Hz), 8.88 (d, 1H, J = 8.1 Hz).; MS (ESI) m/z (%): 285 (M^{++}2, 7), 283 (M+, 21), 105 (100).

4-(2-Bromobenzylidene)-2-phenyl-5(4H)-oxazolone (3g):

Mp. 145; IR (KBr): 1796, 1773 (C=O), 1651 (C=N), 1582, 1556 (C=C).; ^{1}H NMR (300 MHz, DMSO-d6): δ 7.40–7.51(m, 2H), 7.57–7.67 (m, 3H, (2Ar–H + 1CH=C)), 7.74 (d, 1H, J = 7.5 Hz), 7.80 (d, 1H, J = 8.1 Hz), 7.94 (d, 1H, J = 7.2 Hz), 8.14 (d, 1H, J = 7.2 Hz), 8.86 (d, 1H, J = 8.1 Hz).; MS (ESI) m/z (%): 328 (M+, 5.6), 330 (M^{++}2, 4.8), 327 (27.3), 329 (26.9), 248 (59), 105 (100).

4-(3,4-Dimethoxybenzylidene)-2-phenyl-5(4H)-oxazolone (3h):

Mp. 152; IR (KBr): 1789, 1768 (C=O), 1650 (C=N), 1596, 1579 (C=C).;^{1}H NMR (300 MHz, DMSO-d6): δ 3.86 (s, 3H, OMe), 3.88 (s, 3H, OCH3), 7.13 (d, 1H, J = 8.7 Hz), 7.32 (s, 1H, CH=C), 7.60–7.73 (m, 3H), 7.81 (d, 1H, J = 9.0 Hz), 8.08–8.14 (m, 3H).; MS (ESI) m/z (%): 309.15 (M^+, 6.0), 105 (100).

2-Phenyl-4-(3-phenylallylidene)-5(4H)-oxazolone (3i):

Mp. 130; IR (KBr): 1783, 1749 (C=O), 1642 (C=N), 1596, 1574 (C=C).;^{1}H NMR (300 MHz, DMSO-d6): δ 7.27 (d, 1H, CH=C, J = 11.4 Hz), 7.36–7.42 (m, 4H, Ar–H), 7.57–7.68 (m, 7H, (6 Ar–H + 1 CH=C)), 8.08 (d, 1H, CH=C, J = 12.0 Hz).; MS (ESI) m/z (%): 275.10 (M^+, 12.57), 105 (100).

Conclusion

In summary, we have developed a simple, efficient and environmental benign one-pot method for synthesis of azlactones or Oxazolones using a combination of solvent asWater-

PEG catalyzed by sodium acetate under simple conventional technique. The key advantages of this strategy over other conventional, non-conventional methods include its simple, non-hazardous catalyst, solvent as well as its facile work-up, high yield and environmental friendly.

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