

Construction Strategies To Achieve New Supreme Series Of Poly Heterocyclic System Incorporating Arylidene Imidazolone

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Abstract

Poly heterocyclic system received a great deals of attention due to it's wide applications in the pharmacists, and, agrochemical dyes and advance polymers holds, especially when it's involving aza ring such as arylidene imidazolone which are versatile organic unite that well known as core structure in fluorescent proteins, like GFP and as powerful fluorogenic dyes for Cell imaging, Sensors for metal ions (Zn+Cd), as well as, potential anticancer agent due to the tunable photo physical and biological properties. Basically this organic unite used in this work to perform poly heterocyclic system involving 1, 2, 3- oxadiazol, 4- arylidene imidazolone and aryl ring. First of all, the arylidene imidazolone (3&4) were prepared thorough the reaction of arylidene oxazolone (1&2) with semicarbazide in acidic media then it was converted to the corresponding Schiff bases (5&6) via the reaction with p-hydroxy benzaldehyde. These Schiff bases then underwent intracyclization reaction by the action of acetic anhydride to offered the target compounds represented by poly heterocyclic system including both of 4-arylidene imidazolone and 1,3,4 -oxadiazoline (7&8).

Keywords: Imidazolone, 1,3,4-Oxadiazole, Schiff base, Poly heterocyclic ring, Oxazolone

Introduction

Imidazolone is often a heterogeneous five membered ring with two nitrogen atoms and a carbonyl group in position (5). All heterocyclic compounds with imidazole moiety are promising scaffolds for investigating medical potential, as well as it exhibits a wide spectrum as antibacterial (Banoon et al., 2025), antifungal (Muheyuddeen et al., 2024), antiviral (Teli et al., 2022), analgesic (Sharma et al., 2023), antihypertensive (Liu et al., 2025), antioxidant agent (Abu-Jabal et al., 2023) and enzyme inhibiting properties (El-Kalyoubi et al., 2021). Arylidene imidazole are a fascinating class of chemicals that have attracted a lot of research recently due to their numerous biological and chemical actions especially when it includes a substituent in position (1). On the other hand, 1, 3, 4-oxadiazole is another important type of five membered heterocyclic compounds known as a crucial scaffold in medical chemistry for developing drugs with different derivatives that show diverse activities such as anticancer (Smith et al., 2023), antimicrobial (Shaikh et al., 2023), anti-inflammatory (Rai et al., 2024), and antiviral properties (Feng et al., 2021) in addition to its pharmaceutical activity (Summa et al., 2008). In this work and according to the advantages mentioned above, a poly heterocyclic system has been prepared starting from 4-arylidene oxazolone (1&2) (prepared via the reaction between hippuric acid and substituted benzaldehyde in the presence of acetic anhydride) which converted to the N-hydrazino 4-arylidene imidazolone (3&4) via its reaction with semicarbazide and the later was reacted with p-hydroxy benzaldehyde to afford Schiff base (5&6) as an active precursor for preparing 3-acetyl - 1, 3, 4-oxadiazoline via intracyclization reaction in the presence of acetic anhydride. All prepared compounds were illustrated by FT-IR, ¹H-NMR spectroscopy and also by the M.P. and T.LC technique.

Experimental

Melting points (M.P.) were determined using the SMP30-Stuart melting point apparatus. FT-IR spectra were recorded using a Pye Unicam SP 2000. ¹H-NMR spectra were scanned using Bruker Bio Spin GmbH Spectrophotometer (400 MHz) (Turkey) with TMS as the internal standard and DMSO-d₆ as solvent. TLC, glass plates of suitable height (12cm) were used and coated with silica gel 60^oA with gypsum 13% using solvent systems (methanol: benzene) in various ratios (2:8) and (5:5) enhanced with iodine vapor to reveal the spots.

Synthesis of 2-phenyl-4-arylidene -5-oxazolone (1&2): (AL-jbure, 2020)

Equimolar (0.012 mole) of hippuric acid and substituted benzaldehyde was mixed very well then dissolve in (15 ml) ethanol then (2-3 ml) of acetic anhydride was added dropwise for (3 min.) with vigorous stirring, followed by reflux for (3 hrs.). Cooling and adding (20ml) of methanol, then the solution settle for (24 hrs.). The resulting product filtered off and washed thoroughly with cold water followed by recrystallization from ethanol.

- **2-phenyl-4-(3-(4-(dimethylamino)phenyl)allylidene)-5-oxazolone(1)**

Dark brown, M.P.=135-138°C; Yield = 75% ; T.L.C(R_f): 0.648; FT-IR (ν cm⁻¹) : 2082 & 2905 , 1655 , 1596 , 1299 ; H¹-NMR(δ ppm) : 2CH₃ (s,2.819,6H) ; CH=C(d,2.991,1H) ; ph-H (m, 6.563-6.62,5H) ; Ar-H (AB-system) (d-d,6.715-6.735 , 7.539-7.562,4H), Ar-CH=CH-CH:(d,9.523-9.543,1H) .

- **2-phenyl-4-(4-dimethylamino) benzylidene-5-oxazolone (2).**

Yellowish organic powder; M.P.=68-69 °C; yield = 66% ; T.L.C(R_f): 0.510; FT-IR (ν cm⁻¹) : 2794 , 2904 , 1659 , 1532 ; H¹-NMR(δ ppm) : 2(CH₃) :(s, 3.04-3.35,6H) , Ar-H :(m, 6.78 – 6.80,4H), ph-H:(m, 7.68 – 7.70,5H) , CH=C:(s,9.67,1H).

Synthesis of 2-phenyl-4-arylidene -4,5-dihydro-1H-5-imidazolone (3&4) (El-Kalyoubi et al., 2021; Mohamad and Shaymaa, 2020)

In round bottomed flask (50ml) equimolar (0.0125mole) of compound, (1&2) and semi carbazide was dissolved in (25 ml) of ethanol in acidic media (5-10 drops) from glacial acetic acid with stirring for (30 min.) followed by reflux for (3 hrs) . Cooling to room temperature followed by filtration of the resulting product, washed thoroughly with water to remove the excess of acid. The resulting product was then dried and recrystallization from ethanol

- **2-phenyl-4-(3-(4-(dimethylamino)phenyl)allylidene)-4,5-dihydro-1H-5-imidazolone (3):**

Dark orang; M.P.: 64-66°C, Yield= 90%, T.L.C (R_f) : 0.810 ; FT-IR (ν cm⁻¹): 3305 , 3075 , 1662 , 1590 , 1520 , 1480, 1223; H¹-NMR(δ ppm) : NH₂(s,2.872,2H) ; 2CH₃(s, 2.899 , 6H) ; Ar- CH=C (d,6.514-6.538,2H); CH=CH-C (d-d,6.571-6.591,6.610-6.631,1H) ; Ar-H(m,6.631-7.757,9H) ; CH=CH-CH= (d,9.527-9.547,1H) ; NH(s,10.067 , 1H) .

- **2-phenyl-4-(4-dimethylamino) benzylidene-4,5-dihydro-1H-5-imidazolone (4)**

Brite Yellow Powder; M.P. : 217-219°C; Yield: 88% ; T.L.C (R_f) : 0.612 ; FT-IR (ν cm⁻¹) : 3462, 3286, 1660, 1602, 1551, 1528,1231; H¹-NMR(δ ppm) : NH₂(s,2.932,2H) ; 2CH₃(s, 2.986 , 6H) ; Ar-H(m,6372-8.515,9H) ; Ar- CH=C (s,9.672,1H); NH(s,9.986 , 1H).

Synthesis of 2-phenyl-4-arylidene-N-(4-hydroxybenzylidene)-4,5-dihydro-5- imidazolone-1-carbohydrazide (5&6) (Hosseini & Bayat, 2019):

In round bottomed flask (50ml) occupied with magnetic bar, (0.01 mole) of p-hydroxy benzaldehyde was dissolved in (5ml) absolut ethanol with few drops of glacial acetic acid (3drops) then an ethanolic solution of compounds (3&4) was added with stirring for (30min.) followed by reflux for (2 hrs.). The reaction mixture then cooled to room temperature and poured onto beaker containing crash ice with stirring, the resulting precipitate filtered off and washed thoroughly with ice-water, dried and recrystallized from ethanol.

- **2-phenyl-4-(3-(4-(dimethylamino)phenyl)allylidene)-N-(4-hydroxy benzylidene) -4,5-dihydro-5-imidazolone-1-carbohydrazide (5)**

Yellowes plate; M.P. 91-92°C ; Yield: 78%; T.L.C (R_f) : 0.678 ; FT-IR (ν cm⁻¹) : 3490 , 3110 , 1662 , 1593 , 1519 .

- **2-phenyl-4-(dimethylamine) benzylidene)-N-(4-hydroxy benzylidene) -4,5-dihydro-5-imidazolone-1-carbohydrazide (6):**

Orange plate; M.P. : 331-333°C, Yield: 69% ; T.L.C (R_f) : 0.769; FT-IR (ν cm⁻¹) : 3459 , 3281 , 1681, 1594 , 1549.

Synthesis of 1-(4-acetyl-5-(4-hydroxyphenyl)-4,5-dihydro-1,3,4-oxadiazolin-2-yl)-2-phenyl-5-arylidene-3,5-dihydro-5-imidazolone(7&8) (Al-Azzawi & Hammud, 2013; Shaymaa ,2011)

(0.01mole) of Schiff base(6&5) was poured onto round bottomed flask (50ml) then (5-10 ml) of acetic anhydride , was added then the reaction mixture refluxed for (5 hrs) followed by cooling to room temperature than poured onto beaker containing Ice-Water, the resulting product was filtered off and washed thoroughly with ice-water, dried and recrystallized from ethanol.

- **1-(4-acetyl-5-(4-hydroxyphenyl)-4,5-dihydro-1,3,4-oxadiazolin-2-yl)-2-phenyl-5-(3-(4-(dime**

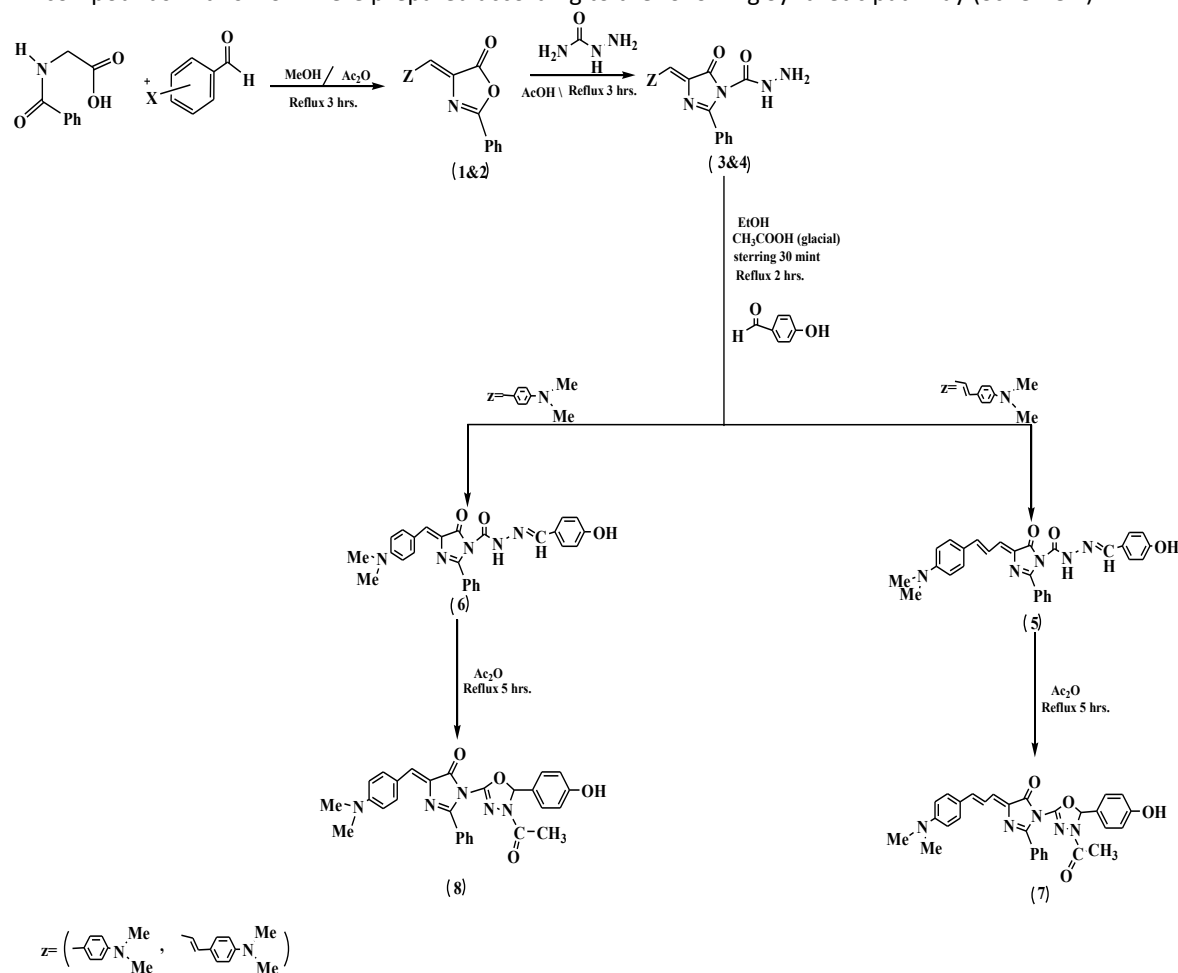
- **thylamino)phenyl)allylidene)-3,5-dihydro-5-imidazolone (7):** Brown powder; M.P.: 95-97°C; Yield:80% ;T.L.C (R_f) : 0.821; FT-IR (ν cm⁻¹) : 3335, 2938, 2820, 1797, 1660, 1589, 1550; H¹-NMR(δ ppm) : 2CH₃(s,1.834,6H) ; CH₃-C=O(s,1.974,3H) ; OH(s,3.049,1H) ; Ar-CH=CH (d-d,6.7-6.8,1H) ; Ar-H(m,7.677-7.699,8H) ; Ar-CH=C (d,9.6-9.8,1H) .

- **1-(4-acetyl-5-(4-hydroxyphenyl)-4,5-dihydro-1,3,4-oxadiazolin-2-yl)-2-phenyl-5-(dimethylamino)benzylidene)-3,5-dihydro-5-imidazolone (8):**

Gray Powder; M.P.: 221-223°C, Yield:74% ; T.L.C (R_f) : 0.688 ; FT-IR (ν cm⁻¹) : 3452, 2932, 2803, 1717, 1699, 1569, 1520; H¹-NMR(δ ppm) : 2CH₃(s,1.836,6H) ; CH₃-C=O(s,1.976,3H) ; OH(s,3.046,1H) ; C=CH (s,9.724,1H) ; Ar-H(m,7.656-7.889,8H) .

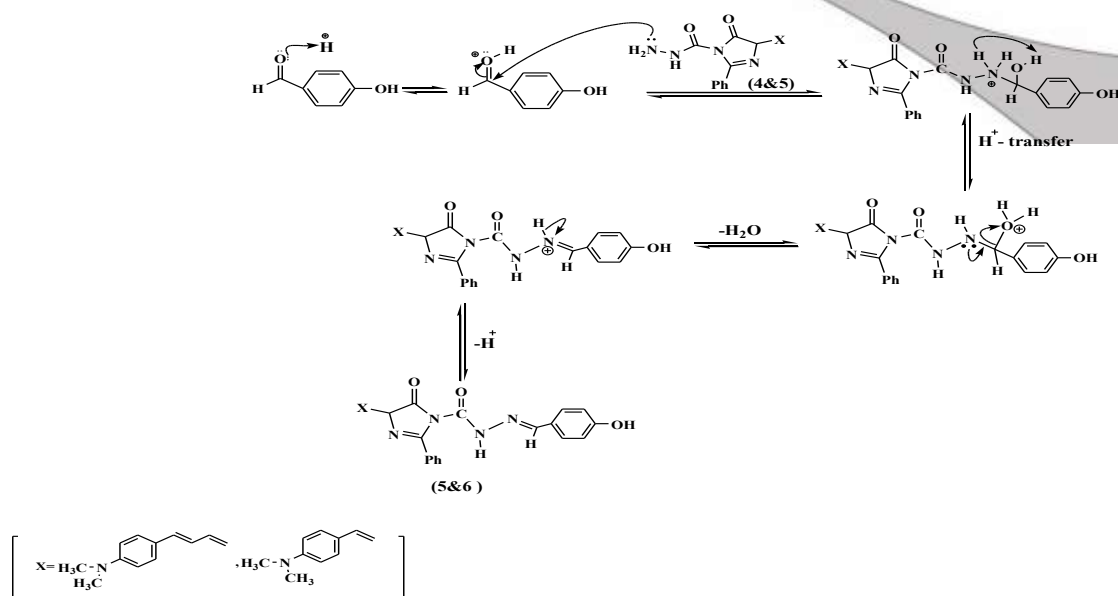
Results and Discussions

All compounds in this work were prepared according to the following Synthetic pathway (Scheme 1):



Scheme (1)

First of all, the arylidene -5, imidazalene (3 & 4) were prepared through the following mechanism, (Scheme 2), which involving the nucleophilic attack from the ion pair of amino group of semicarbazide to give the intermediate (I) which then underwent intracyclization process with losing of water molecule to achieve the 4-arylidene imidazolone (3&4).



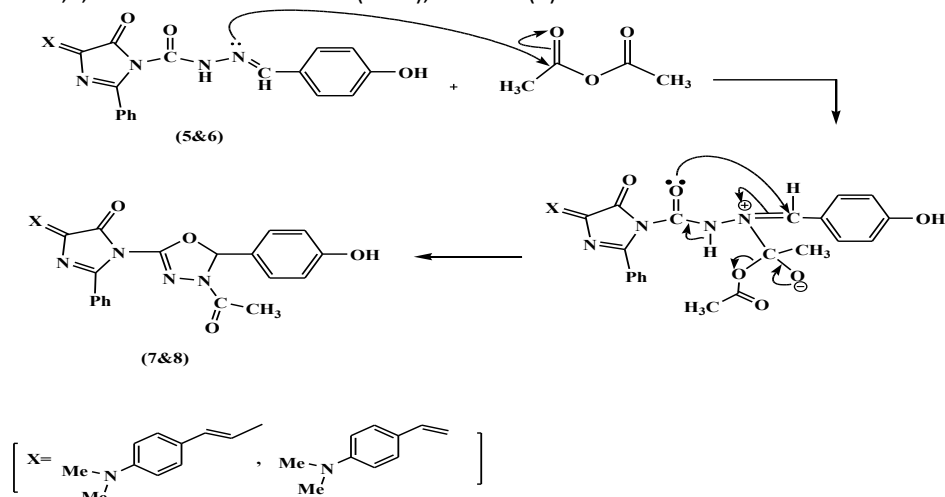
Scheme (3)

In FT-IR spectroscopy the disappearing of the stretching vibration of NH_2 and the presented of $\text{C}=\text{N}$ stretching vibration at $(1549\text{-}1519\text{ cm}^{-1})$ Table (2), gave a preliminary proof about the predicted composition, and also the absence of NH_2 protons peak in $^1\text{H-NMR}$ came up exactly as expected, Table (2).

Table (2) :- The FT-IR data for compounds (5&6)

Comp. No.	X	FT-IR (KBr), ν (cm^{-1})				
		OH	NH	C=O	C=C	N=C
5	p-(CH_3) ₂ N cinnamaldehyde	3490	3110	1662	1593	1519
6	p-(CH_3) ₂ N benzaldehyde	3459	3281	1681	1594	1549

Finally, compounds (5 & 6) were suffered from intracyclization reaction in presence of acetic anhydride to perform the 1,3,4-oxadiazole derivatives (7& 8), Scheme (4).



Scheme (4)

Actually, in $^1\text{H-NMR}$, the appearance of another singlet peak at (1.974 and 1.976 ppm) refer clearly to the methyl acetyl group and the absence of singlet peak for NH protons come with agreement with the suggested structure Table (3) . On the other hand, in FT-IR these two compounds shown two type of absorption bands refer to the two types of carbonyl group once at (1660-1699 cm^{-1}) refer to the amide carbonyl group and the other band at (1717-1797 cm^{-1}) refer to the carbonyl in the imidazole ring . So these spectra identify the formation product and proof the suggested structure .

Table (3) :- The FT-IR data for compounds (7&8)

Comp. No.	x	FT-IR (KBr), ν (cm ⁻¹)							¹ H-NMR, DMSO-d ₆ , δ (ppm)
		OH	C=O Lactam	C=O amid	C=C	N=C	CH ₃		
							asym	sym	
7	$\text{p}-(\text{CH}_3)_2\text{N}$ cinnamaldehyde	3335	1797	1660	1589	1550	2938	2820	2CH ₃ (s,1.834,6H) ; CH ₃ C=O(s,1.974,3H) ; OH(s,3.049,1H) ; ArCH=CH (d-d,6.7-6.8,1H) ; CH=CH-C (d-d,7.8-8.0 ,8.8- 8.9,1H) ; Ar-H(m,7.677- 7.699,8H) ; CH-CH=C (d,9.6-9.8,1H)
8	$\text{p}-(\text{CH}_3)_2\text{N}$ benzaldehyde	3452	1717	1699	1569	1520	2932	2083	2CH ₃ (s,1.836,6H) ; CH ₃ C=O(s,1.976,3H) ; OH(s,3.046,1H) ; C=CH (s,9.724,1H) ; Ar- H(m,7.656-7.889,8H)

Conclusion

1. Oxadiazolone act as active precursor to achieve divers heterocyclic compounds through easier ring converting from oxazole to imidazole without further purification and easier working out
2. The synthetic method of imidazolone was very fast and simple and also it act as active core to achieve another type heterocyclic compounds.
3. No complex procedures with available catalysts and starting material made this work very interesting

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