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One Pot Synthesis and Antibacterial Activity of (4*Z*)-4-Benzylidene-1-methyl-2-styryl-1*H*-imidazol-5(4*H*)-one

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Green synthesis of (4*Z*)-4-benzylidene-1-methyl-2-styryl-1*H*-imidazol-5(4*H*)-one derivatives have been developed in good yields and tested for their antibacterial activities against *Escherichia coli, Providencia aeruginosa*, *Pseudomonas azotogensis* and *Baccilus subtillis.* Some of the synthesized compounds possess good activity against *Escherichia coli* and *Baccilus Subtillis* compared to standard drug streptomycin.

Keywords: Green synthesis, Schiff bases, Antibacterial activity.

INTRODUCTION

The increasing resistance of human pathogens to current antimicrobial agents is a serious medical problem. Many of the drugs currently available have undesirable effects and might be toxic. Considering the fact that the available antimicrobial agent originate from a limited number of sources and that most of them have similar modes of activity. It is very important to explore additional sources for substances with potential antimicrobial activity, which could possibly have different modes of activity or affect different sites in the bacterial and fungal cells. Imidazole and its derivative are of great significance due to their important roles in biological system. The synthesis of newer class of antibacterial and antifungal agents is in need of time, especially against drug-resistant bacteria and fungi, such as Gram-positive and Gram-negative strains, which are responsible for a number of serious infections in the acute and chronic care units in hospitals.

Imidazolinone ring system is of biological and chemical interest since long. The imidazolinone units are found in many biologically active compounds. The imidazolones compounds having diverse bioactivities including anticancer [1], anti-HIV agents [2], anticonvulsant [3,4], monoaminooxidase (MAO) inhibitory [5], antiparkinsonian [6,7], CNS depression [8], antimicrobial [9-12], anthelmintics [13], *etc*.

Schiff bases in heterocyclization can act as hydrogen acceptors. Proton acceptor-donor catalyst L-tyrosine has been playing a vital role in synthetic organic chemistry [14]. Amino acids have emerged as an efficient and important catalyst in several transformations such as aldol reactions [14], conjugate addition [15], additions to imines and nitro-alkenes [16]. This prompted us to synthesize (4*Z*)-4-benzylidene-1-methyl-2-styryl-1*H*-imidazol-5(4*H*)-one derivatives of derivatives and evaluate them for antibacterial activity.

EXPERIMENTAL

Melting points are uncorrected and taken in open capillary tubes in sulphuric acid bath. TLC was run on silica gel-G and visualization was done using UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as internal standard with 400 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 value only.

Preparation of (*Z*)-2-acetamido-N-methyl-3-phenyl-acrylamides: A mixture of **1a-1b** (10 mM) and methylamine (10 mM) was added in ethanol for 5 h at 80 °C. The completion of the reaction was checked by TLC, then this reaction mixture was cooled to room temperature and poured into ice-cold water (50 mL). The solid separated out was collected, washed with water (10 mL) and dried. The product was recrystallized from ethanol to obtain **2a-2b**.

Preparation of (4*Z*)-4-benzylidene-1-methyl-2-styryl-1*H*-imidazol-5(4*H*)-one derivatives 6(a-l): Equimolar quantities of **2(a-b)** (10 mM) and Schiff bases **3(a-f)** (10 mM) were mixed together in 20 mL of EtOH in the presence of L-tyrosine (1 mM) as catalyst. The mixture was refluxed for 2 h. The completion of the reaction was checked by TLC, then this

reaction mixture was cooled to room temperature and poured into ice-cold water (50 mL). Solid separated out which was collected, washed with water (10 mL) and dried. The product was recrystallized from ethanol to obtain products **6(a-l)**.

Compound 6a: m.f.: $C_{19}H_{16}N_2O$; m.p.: 182-184 °C; yield: 75 %; IR (KBr, ν_{max}, cm^{-1}): 303 (Ar), 2958 (-C**H**$_3$), 1661 (-C=O) 1625 (-C=C) 1199 (-C=N); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.3 (s, 3H, -C**H**$_3$), 7.4-8.0 (m, 10H, Ar-**H**) δ8.O, 8.4, D (2H (-CH=CH) and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 110 (-C=C), 119 (-C=C), 122 (-C=C) Ar, 138.2 (C-N), 150.9 (-C=N), 162.8 (>C=O). M+H = 291.

Compound 6b: m.f.: $C_{20}H_{19}N_2O_2$; m.p.: 195-197 °C; yield: 70 %; IR (KBr, ν_{max}, cm^{-1}): 1665 (-C=O); 1199 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.3 (s, 3H, -C**H**$_3$), 4.5 (s, 3H, -C**H**$_3$), 7.4-8.3 (m, 9H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 111.1 (-C=C), 118.8 (-C=C), 122.7 (-C=C) Ar, 138.4 (C-N), 145.9 (-C=N), 164.3 (>C=O). M+H = 321.

Compound 6c: m.f.: $C_{19}H_{16}N_2OF$; m.p.: 180-182 °C; yield: 65 %; IR (KBr, ν_{max}, cm^{-1}): 1670 (-C=O), 1199 (C-N), 1050 (-C=F); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.4 (s, 3H, -C**H**$_3$), 7.4-8.4 (m, 9H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 110.4 (-C=C), 118.2 (-C=C), 122.3 (-C=C) Ar, 138.5 (C-N), 152.8 (-C=N), 160.7 (>C=O) M+H = 310.

Compound 6d: m.f.: $C_{19}H_{16}N_3O_3$; m.p.: 210-212 °C; yield: 60 %; IR (KBr, ν_{max}, cm^{-1}): 1661 (-C=O), 1199 (C-N), ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.3 (s, 3H, -C**H**$_3$), 7.4-8.3 (m, 9H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 110 (-C=C), 119 (-C=C), 122 (-C=C) Ar, 138.2 (C-N), 150.9 (-C=N), 162.8 (>C=O) M+H = 337.

Compound 6e: m.f.: $C_{19}H_{16}N_2OCl$; m.p.: 189-191 °C; yield: 55 %; IR (KBr, ν_{max}, cm^{-1}): 1680 (-C=O); 725 (-C=Cl); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.0 (s, 3H, -C**H**$_3$), 7.4-8.5 (m, 9H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 112.2 (-C=C), 119.3 (-C=C), 122.3 (-C=C) Ar, 138.5 (C-N), 143.9 (-C=N), 160.3 (>C=O), M+H = 326.

Compound 6f: m.f.: $C_{19}H_{16}N_2OCl$; m.p.: 220-222 °C; yield: 50 %; IR (KBr, ν_{max}, cm^{-1}): 1690 (-C=O), 1200 (C-N), 725 (-C=Cl); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.2 (s, 3H, -C**H**$_3$), 7.4-8.3 (m, 9H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 110.3 (-C=C), 118.6 (-C=C), 123.4 (-C=C) Ar, 138.3 (C-N), 145.6 (-C=N), 160.6 (>C=O) M+H = 325.2.

Compound 6g: m.f.: $C_{19}H_{16}N_2OCl$; m.p.:195-197 °C; yield: 70 %; IR (KBr, ν_{max}, cm^{-1}): 1694 (-C=O); 1199 (C-N), 725 (-C=Cl); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.3 (s, 3H, -C**H**$_3$), 7.4-8.3 (m, 9H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 112.5 (-C=C), 118.9 (-C=C), 122.3 (-C=C) Ar, 138.4 (C-N), 150.4 (-C=N), 161.4 (>C=O) M+H = 326.

Compound 6h: m.f.: $C_{20}H_{19}N_2O_2Cl$; m.p.: 182-185 °C; yield: 70 %; IR (KBr, ν_{max}, cm^{-1}): 1660 (-C=O) 1199 (C-N), 725 (-C=Cl); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.2 (s, 3H, -C**H**$_3$), 4.4 (s, 3H, -C**H**$_3$), 7.4-8.3 (m, 8H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 110.2 (-C=C), 118.5 (-C=C), 122.2 (-C=C) Ar, 138.3 (C-N), 146.3 (-C=N), 164.2 (>C=O) M+H = 357.

Compound 6i: m.f.: $C_{19}H_{16}N_2OFCl$; m.p.: 218-220 °C; yield: 65 %; IR (KBr, ν_{max}, cm^{-1}): 1673 (-C=O), 1200 (C-N), 725 (-C=Cl); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.3 (s, 3H, -C**H**$_3$), 7.4-8.4 (m, 8H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 111.3 (-C=C), 118.8 (-C=C), 122.2 (-C=C) Ar, 138.6 (C-N), 150.7 (-C=N), 162.8 (>C=O) M+H = 345.

Compound 6j: m.f.: $C_{19}H_{16}N_3O_3C1$; m.p.: > 230 °C; yield: 65 %; IR (KBr, ν_{max}, cm^{-1}): 1661 (-C=O)1200 (C-N), 725 (-C=Cl); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.3 (s, 3H, -C**H**$_3$), 7.4-8.3 (m, 10H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 112.2 (-C=C), 118.6 (-C=C), 122.1 (-C=C) Ar, 138.2 (C-N), 150.9 (-C=N), 162.8 (>C=O) M+H = 372.

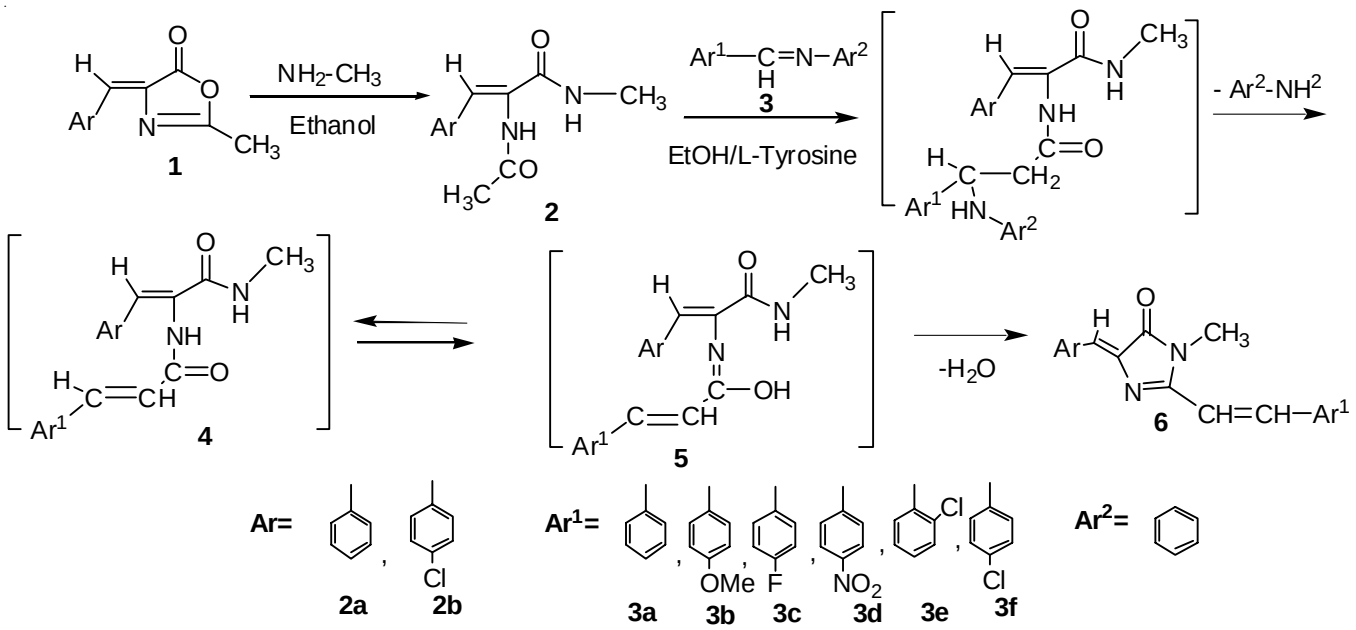
Compound 6k: m.f.: $C_{19}H_{16}N_2OCl_2$; m.p.: 222-224 °C; yield: 55 %; IR (KBr, ν_{max}, cm^{-1}): 1690 (-C=O), 1199 (C-N), 725 (-C=Cl); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.3 (s, 3H, -C**H**$_3$), 7.4-8.5 (m, 8H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 111.2 (-C=C), 119 (-C=C), 123.3 (-C=C) Ar, 138.5 (C-N), 144.6 (-C=N), 162.5 (>C=O) M+H = 362.

Compound 6l: m.f.: $C_{19}H_{16}N_2OCl_2$; m.p.: > 230 °C; yield: 60 %; IR (KBr, ν_{max}, cm^{-1}): 1685 (-C=O), 1199 (C-N), 725 (-C=Cl); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.2 (s, 3H, -C**H**$_3$), 7.4-8.5 (m, 8H, Ar-**H** and s, 3H, =C**H**-Ar), ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 110.2 (-C=C), 118.6 (-C=C), 125.7 (-C=C) Ar, 138.9 (C-N), 143.9 (-C=N), 165.7 (>C=O) M+H = 362.

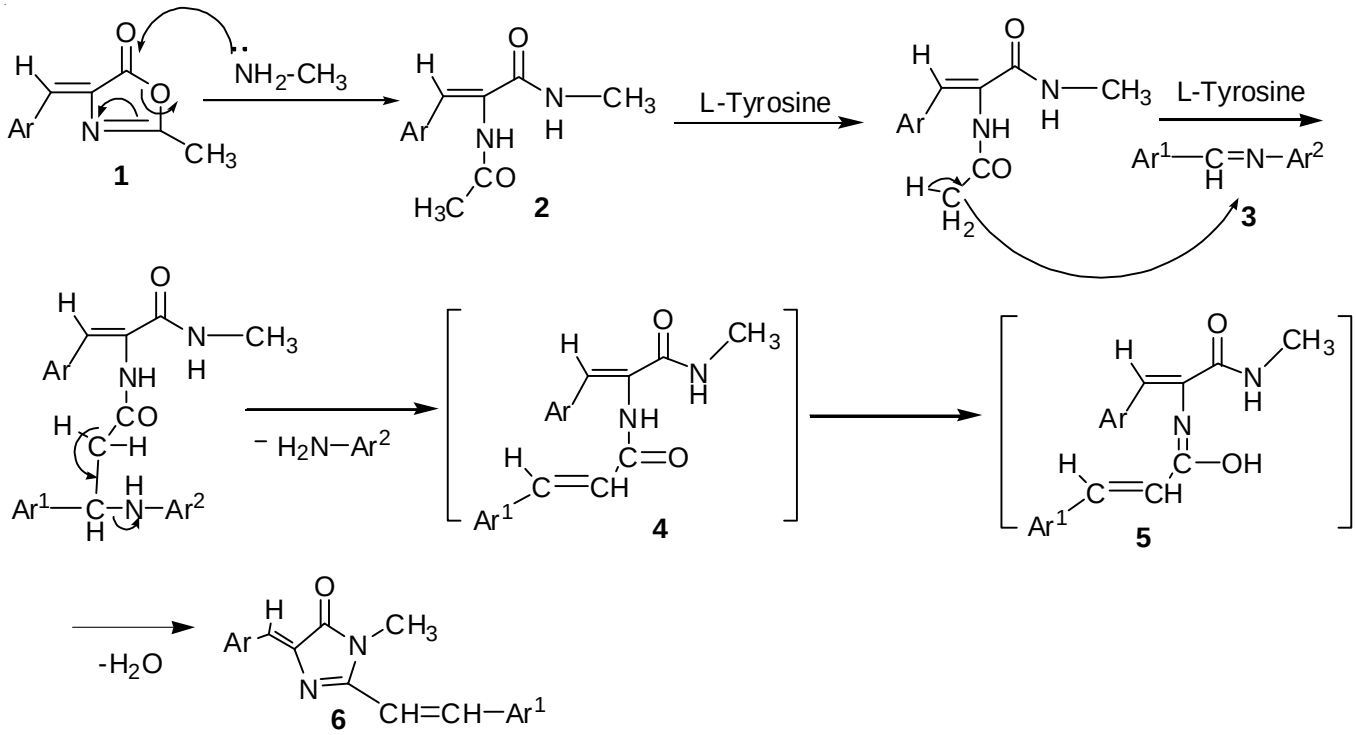
RESULTS AND DISCUSSION

Title compounds (4*Z*)-4-benzylidene-1-methyl-2-styryl-1*H*-imidazol-5(4*H*)-one derivatives **6(a-l)** have been synthesized by green approach through synthetic sequence shown in **Scheme-I**. Initially, the azalactone (*Z*)-4-benzylidene-2-methyl-oxazol-5(4*H*)-one (**1**) was treated with methylamine and refluxed for 5 h in ethanol to produce (*Z*)-2-acetamido-N-methyl-3-phenylacrylamides **2(a,b)** (**Scheme-I**). Compounds **2(a,b)** were reacted with the Schiff bases benzylidine/substituted benzylidine anilines (**3a-f**) in the presence of L-tyrosine as a catalyst in the presence of ethanol under reflux condition for 2 h to produce *in situ* (4*Z*)-4-benzylidene-1-methyl-2-styryl-1*H*-imidazole-5(4*H*)-ones **6(a-l)**. A reasonable mechanism has been formulated for the formation of these imidazoline 5-ones. The mass spectrum of the compound **6a** showed the molecular ion peak at *m/z* 291 corresponding to molecular formula. The IR spectrum of the compound showed the absence of absorption for –NH group at 1662 cm^{-1} and the ^{1}H NMR (DMSO-d_6) lacked signals for methyl protons of acetamido group, instead two trans olefinic protons were observed at δ 8.0 and δ 8.4 along with additional signals for aromatic compounds. This data conforms the structure of **6a** and in the similar way the structures of **6(b-l)** were confirmed.

The mechanism of the reaction is rationalized as the styrilation of acetamido group of **2** followed by dehydration. The mechanism can be explained as Michael type addition of the active methyl group **2** across the carbon-nitrogen double bond of the Schiff base **3** leading to the generation of styryl



Scheme-I



Scheme-II

group by the loss of aniline. The resulting unstable intermediates **4** and **5** readily undergoes dehydrative cyclization to form stable imidazolin-5-one derivative **6(a-l)** (**Scheme-II**).

in vitro **Antibacterial activity:** The synthesized compounds [**6(a-l)**] were screened for their *in vitro* antibacterial activity aganist *Escherichia coli* (NCIM 2065), *Providencia aeruginosa* (NCIM 2200), *Pseudomonas azotogensis* (NCIM 2075) and *Baccilus subtillis* (NCIM 2063). Antibacterial activity of compounds was evaluated using agar-well diffusion method [17]. The petri plates were sterilized using an autoclave at 120 °C for 30 min. A petri-dish of 100 mm diameter was filled with 50 mL of freshly prepared Nutrient Agar media and allowed to solidify. Different bacterial species were inoculated on to the medium by streak plate method. The plates were incubated at 30 °C temperature and zone of inhibition was measured after 24 h. The standard used for determining the antibacterial activity is streptomycin. The compounds were dissolved in DMF and activity described at 100 µg/mL level. From the data presented in Table-1, it is clear that compounds **6c, 6e, 6f, 6i, 6k** and **6l** possess good activity against *Escherichia coli* and *Baccilus Subtillis*. Other compounds exhibited moderate antibacterial activity against *E. coli*. However, all compounds showed moderate activity against, *Providencia aeruginosa* and *Pseudomonas azotogensis* (Table-1).

TABLE-1
ANTIBACTERIAL ACTIVITY OF COMPOUNDS **6(a-l)**

Compd.	*Escherichia coli*	*Providencia aeruginosa*	*Pseudomonas azotogensis*	*Baccilus subtillis*
6a	8	10	9	10
6b	9	7	9	13
6c	22	14	12	20
6d	11	15	9	10
6e	20	8	10	21
6f	22	3	11	21
6g	8	10	8	10
6h	12	8	10	14
6i	23	12	13	19
6j	8	3	7	12
6k	18	9	9	18
6l	22	10	9	19
SD	30	32	28	30

SD = Standard drug: Streptomycin

Conclusion

One pot green synthesis for the preparation of imidazolone derivatives **6(a-l)** in high purity and excellent yields with moderate antibacterial activity **6(a-l)** has been developed by making use of L-tyrosine as catalyst.

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