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Synthesis and Characterization of Some Novel Biphenyl-4-carboxylic Acid (4-Benzylidene-5-oxo-2-subsituted phenyl-4,5-dihydro-imidazol-1-yl)amide

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Imidazolinone derivatives of **4a-h** have been prepared by the condensation of biphenyl-4-carboxylic acid hydrazide (**2**) with 5-oxazolone derivatives, which were prepared by Erlenmeyer condensation of benzoyl glycine with different aldehydes in presence of sodium acetate and acetic anhydride. The compounds **3a-h** was further reacted with biphenyl-4-carboxylic acid hydrazide (**2**) to give **4a-h** in basic condition. The constitution of the products has been supported by IR, ^{1}H NMR, ^{13}C NMR mass spectra and elemental analysis data.

Key Words: Synthesis, Biphenyl-4-carboxylic acid hydrazides, Antibacterial activity.

INTRODUCTION

A class of small heterocycles called oxazolones which are important intermediates in the synthesis of several small molecules including amino acids, peptides[1-3], antimicrobial or antitumor compounds[4,5], heterocyclic precursors[6-8] as well as biosensors coupling and photosensitive composition devices for proteins[9]. Some oxazolones showed a wide range of pharmaceutical properties[10]. 5-Oxazolones are synthesized by the Erlenmeyer condensation as reported in the literature[11].

Literature survey reveals that the various imidazolinone derivatives possess a broad spectrum of activities which are reflected by their use as anticonvulsant[12] and anti-parkinsonian agents[13]. Some novel imidazolinones have been synthesized by using different oxazolones and condensing them with aliphatic and aromatic amines[14,15] and with sulphonamide as anticonvulsant agents[16].

Several biphenyl acids are marketed as antiinflammatory drugs such as (1,1'-biphenyl)-4-acetic acid[17], γ-oxo(1,1'-biphenyl)-4-butanoic acid[18], α-ethyl-(1,1'-biphenyl)-4-acetic acid[19]. Antiinflammatory activity of biphenyl acid[20] such as 2-fluoro biphenyl acid derivatives, which were useful intermediates for many analgesics and antiinflammatory agents.

Similarly, 3-aryl-2-(1,1'-biphenyl-4-yl)-3-hydroxy-propionic acid[21] having anti-inflammatory activity were synthesized by reacting substituted benzaldehyde with biphenyl acetic acid dianion. Heteroaroyl biphenyl amides compound are also reported

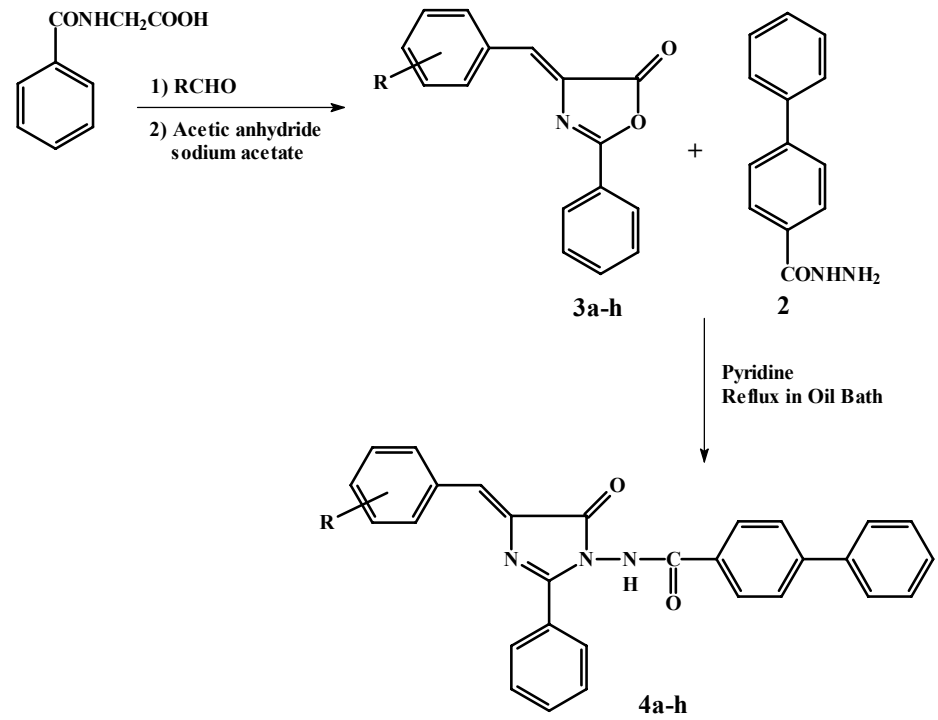
as agrochemical and industrial fungicides[22]. Several anti-hypertensive agents having biphenyl moiety incorporated with imidazole[23,24], pyrrole[25], triazole and other compounds have been reported.

In this paper, the key intermediate biphenyl carboxylic acid hydrazide has been synthesized from ester by the method of Bernstein[26]. The synthesis of biphenyl-4-carboxylic acid hydrazide (**2**) and various 5-oxazolones (**3a-h**) to yield novel imidazolinones (**4a-h**) have also been reported.

EXPERIMENTAL

The melting points were determined in open capillary tubes and are uncorrected. The chemicals and solvents used were of laboratory grade and solvents were purified. Completion of the reaction was monitored by TLC silica gel GF_{254} (E Merck). The final products were purified by column chromatography using silica gel in increasing percentage of ethyl acetate in carbon tetrachloride. IR were recorded on a Shimadzu-8400 FT-IR spectrometer, ^{1}H NMR spectra on a Bruker spectrometer (300 MHz) using TMS as a internal standard (chemical shift in δ ppm) in $CDCl_3$ and DMSO-d_6 and mass spectra were recorded on Hewlett-Packard 5989, LC-MS on Perkin-Elmer API 165. All the synthesized compounds gave satisfactory C, H, N analyses on Perkin-Elmer (U.S.A) 2400 Series.

Preparation of 4-arylidene-2-phenyl-5-(4*H*)-oxazolones (3a-h): 4-Arylidene-2-phenyl-5-(4*H*)-oxazolones were prepared according to the reported method[11].



Preparation of biphenyl-4-carboxylic acid hydrazide (2): Hydrazine hydrate (80 %) (0.4 mol) and 20 mL methanol were taken in a three necked flask, fitted with mechanical stirrer and reflux condenser. The methyl 1,1'-biphenyl-4-carboxylate (0.2 mol) was added slowly in portions with in 15 min. Refluxing was continued for 3 h. Excess methanol was distilled off. Reaction mixture was cooled and solid mass obtained was isolated by filtration, dried and recrystallized from ethanol. Purity of white crystals of bipheny-l-4-carboxylic acid hydrazide having m.p. 178 °C was checked by TLC. Yield 63 %; TLC (methanol:toluene, 2:8, R_f = 0.20). Anal. found (%): C, 73.22; H, 5.40; N, 13.20. $C_{13}H_{12}N_2O$ requires C, 73.58; H, 5.66; N, 13.21 %; IR(KBr, ν_{max}, cm^{-1}): 3326 (NH amine), 3276 (-NH_2), 3021 (Aromatic C-H stretch), 1622 (N-C=O); ^{1}H NMR ($CDCl_3$): δ 7.35 (m, 9H, Ar-H), 5.85 (bs, 1H, -NH), 3.47 (bs, 2H, -NH_2); MS: m/z (%) 212 (73, M^+), 177 (10.1), 165 (20.2), 152 (100).

General procedure for the preparation of biphenyl-4-carboxylic acid (4-benzylidene-5-oxo-2-subsituted phenyl-4,5-dihydroimidazol-1-yl)amide (4a-h): A solution of 2-phenyl-4-benzylidene-5-oxazolone (2.49 g, 0.01 mol) was heated with an equimolar quantity of biphenyl-4-carboxylic acid hydrazide **2** (0.01 mol) in pyridine on oil bath at 140 °C for 4 h. The resulting mass was taken in an organic solvent and refluxed for 6 h with continuous removal of water, cooled, excess solvent removed under vacuum. The resultant solid was worked up and purified over a column of silica gel and the solid recrystallized from suitable solvent, to get 5-imidazolinone and was found chromatographically homogeneous. TLC (ethyl acetate: carbon tetrachloride, 7:3).

Biphenyl-4-carboxylic acid (4-benzylidene-5-oxo-2-(4-methoxyphenyl)-4,5-dihydroimidazol-1-yl)amide (4a): Orange crystals. Yield 68 %, m.p. 182 ºC; TLC (ethyl acetate:carbon tetrachloride, 7:3, R_f = 0.60). Anal. Found: C, 76.29; H, 4.03; N, 8.74. $C_{30}H_{23}O_3N_3$ requires C, 76.11; H, 4.86; N, 8.88%; IR (KBr, ν_{max}, cm^{-1}): 3359 (NH), 3008 (Ar C-H), 2964 and 2852 (CH_3, C-H), 1745 (C=O), 1681 (NH-C=O), 1506, 1361 (C-N), 1261, 1026 (C-O); ^{1}H NMR ($CDCl_3$): δ 8.67 (s, 1H, -NH), 7.75 (d, *J* = 7.60 Hz, 4H, 4-OCH_3 phenyl ring), 7.52-6.78 (m, 14H, Ar-H), 6.90 (d, *J* = 7.75 Hz, 2H, 4-OCH_3 phenyl protons), 6.75 (s, 1H, Ph-C=CH), 3.75 (s, 3H, -OCH_3); MS: m/z (%) 443.2 (M^+).

TABLE-1
PHYSICAL DATA FOR COMPOUNDS **4a-h**

Compd.	R	m.p. (ºC)	Yield (%)	m.f.	Colour	R_f value
4a	4-OCH_3	182	68	$C_{30}H_{23}N_3O_3$	Orange	0.60
4b	4-Cl	160	67	$C_{29}H_{20}N_3O_2Cl$	colourless	0.58
4c	4-OH	184	60	$C_{29}H_{21}N_3O_3$	colourless	0.45
4d	4-F	178	61	$C_{29}H_{20}N_3O_2F$	colourless	0.59
4e	4-N (CH_3)$_2$	158	70	$C_{31}H_{26}N_4O_2$	Red colour	0.50
4f	3-OCH_3, 4-OH	126	65	$C_{30}H_{23}N_3O_4$	Light red	0.44
4g	3, 4, 5-OCH_3	155	68	$C_{32}H_{27}N_3O_5$	Faint yellow	0.61
4h	H	172	60	$C_{29}H_{21}N_3O_2$	colourless	0.60

RESULTS AND DISCUSSION

The structure of all the compounds were confirmed by IR, ^{1}H NMR and elemental analyses. ^{1}H NMR spectra of **2** showed peak at δ 3.47 was assigned the -NH_2 group and showed -NH proton shifted to downfield at 5.85. Mass spectra showed molecular ion peask at 212 and base peak at 152.

Infrared spectra of **4a** showed the -NH band at 3359 cm^{-1} and two bands at 1745 cm^{-1} (C=O) and 1681 cm^{-1} (NH-C=O) which correspond to the carbonyl in 5-imidazolone and the carbonyl of amide, which indicated the presence of two carbonyl group. (C-N) band at 1506 and 1361 cm^{-1}. In the NMR spectra of **4a** the -NH proton shifted downfield at δ 8.67, which is due to the C=O and hetrocyclic ring system in close vicinity. Such downfield of the -NH proton is reported by researcher[27]. The benzylidene proton gave a singlet at δ 6.75 and -OCH_3 proton gave a singlet at δ 3.75. The other entire proton were obtained in the aromatic region. Molecular ion peak showed at 443 which is confirmed its molecular weight. This type of synthesis is reported by Bhatt *et al.*[28].

TABLE-2
SPECTRAL AND ELEMENTAL DATA FOR **4a-h**

Compd.	R	Found (calcd. (%)			^{1}H NMR ($CDCl_3$ and DMSO-d_6)
		C	H	N	
4a	4-OCH_3	76.29 (76.11)	4.03 (4.86)	8.74 (8.88)	δ 8.67 (s, 1H, -NH), 7.75 (d, *J* = 7.60 Hz, 4H, 4-OCH_3 phenyl ring), 7.52-6.78 (m, 14H, Ar-H), 6.90 (d, *J* = 7.75 Hz, 2H, 4-OCH_3 phenyl proton), 6.75 (s, 1H, Ph-C=CH), 3.75 (s, 3H, -OCH_3)
4b	4-Cl	72.12 (72.88)	4.15 (4.19)	8.70 (8.79)	δ 8.52 (s, 1H, -NH), 7.88-6.80 (m, 14H Ar-H + 4H, 4-Cl phenyl ring), 6.55 (s, 1H, Ph-C=CH)
4c	4-OH	75.98 (75.82)	4.72 (4.58)	9.10 (9.15)	δ 8.62 (s, 1H, -NH), 7.8-6.90 (m, 14H, Ar-H + 4H, 4-OH phenyl ring), 6.33 (s, 1H, Ph-C=CH), 3.40 (s, 1H, -OH)
4d	4-F	75.60 (75.65)	4.32 (4.35)	9.10 (9.13)	δ 8.49 (s, 1H, -NH), 7.82-6.93 (m, 14H, Ar-H + 4H, 4-F phenyl ring), 6.45 (s, 1H, Ph-C=CH)
4e	4-$N(CH_3)_2$	76.80 (76.54)	5.29 (5.35)	11.49 (11.52)	δ 8.70 (s, 1H, -NH), 7.95-6.96 (m, 14H, Ar-H + 4H, 4-N, N, dimethyl amino phenyl ring), 6.38 (s, 1H, Ph-C=CH), 3.65 (s, 6H, -N $(CH_3)_2$)
4f	3-OCH_3, 4-OH	73.95 (73.61)	4.74 (4.70)	8.69 (8.58)	δ 8.49 (s, 1H, -NH), 7.82-6.90 (m, 14H, Ar-H + 3H, 3-OCH_3 4-OH phenyl ring), 6.42 (s, 1H, Ph-C=CH), 3.84 (s, 3H, -OCH_3), 3.40 (s, 1H, -OH)
4g	3,4,5-OCH_3	72.30 (72.03)	5.20 (5.10)	7.94 (7.88)	δ 8.52 (s, 1H, -NH), 7.79-7.19 (m, 14H, Ar-H + 2H 3, 4, 5-OCH_3 phenyl ring), 6.57 (s, 1H, Ph-C=CH), 3.84 (s, 9H, -OCH_3)
4h	H	78.65 (78.56)	4.70 (4.74)	9.60 (9.48)	δ 8.66 (s, 1H, -NH), 7.8 (m, 19H, Ar-H) 6.25 (s, 1H, Ph-C=CH)

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