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CHEMISRTY OF NOVEL SPIRO OXAZOLO-THIADIAZOLES DERIVATIVES – SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION

Vijay V. Dabholkar*, Abhishek Karekar, Prem Naik & N. B. Shinde

Organic Research Laboratory, Department of Chemistry,
Mumbai University, K.C. College, Churchgate, Mumbai-400 020, India
E-mail: vijaydabholkar@gmail.com
karekar.abhi@gmail.com

Abstract:
A series of novel 2-N-acetyl hydrazino,4-acetyl,7-phenyl,9-(substitutedbenzylidine),1-thia, 3,4,8,triaza,6-oxa Spiro[4.4] nona-2,7-diene (4) were synthesized and screened for their antibacterial activity. The structures of the products were confirmed by IR, ^{1}H, ^{13}C NMR and elemental analysis.

Key Words: Oxazoles, Thiadiazoles, Aromatic aldehydes, Hippuric Acid, Azalactones.

Introduction:

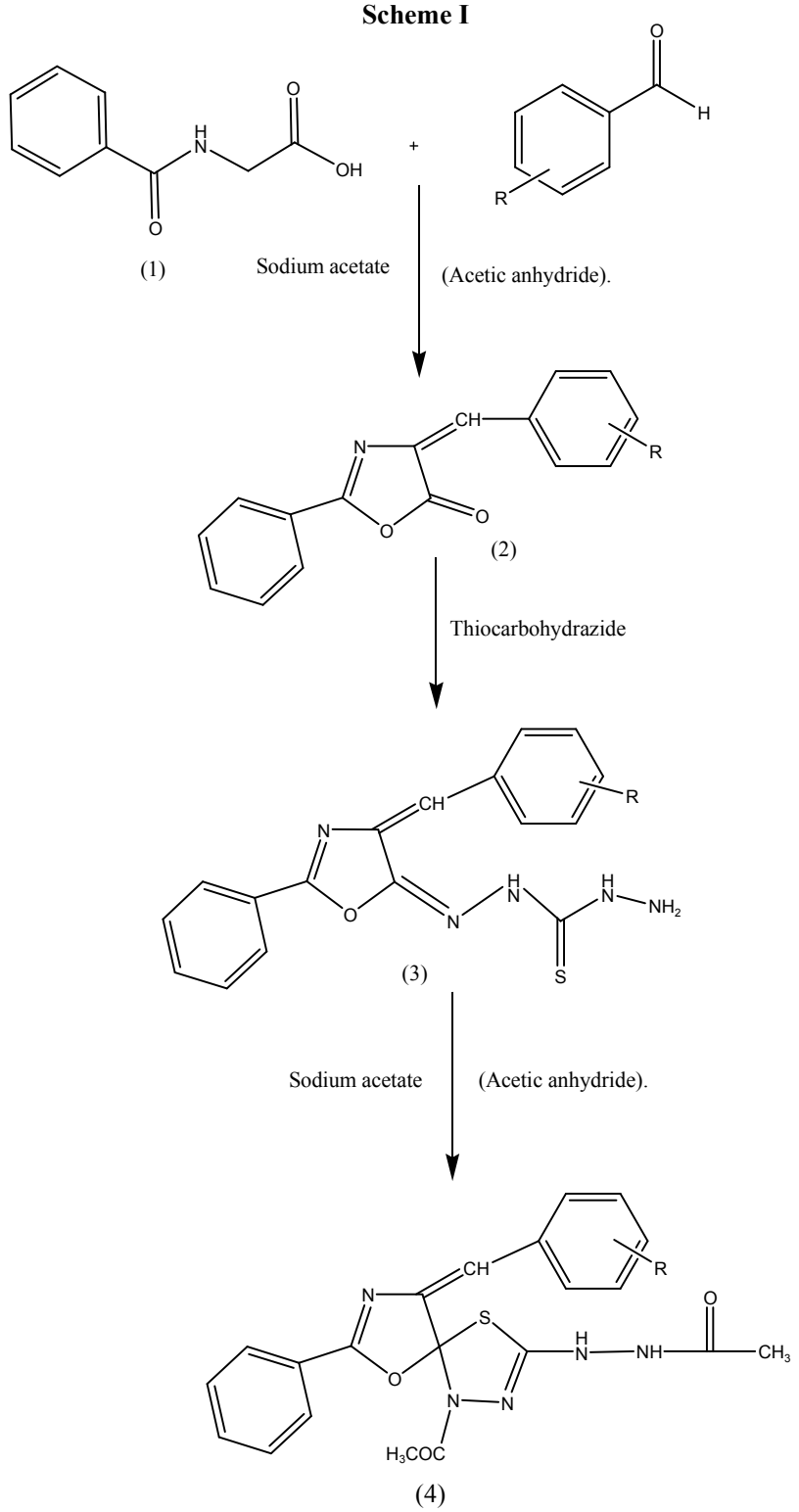
The thiadiazoles have occupied an important place in drug industry. 1, 3, 4-Thiadiazoles have wide applications in many fields. The earliest uses were in the pharmaceutical area as an antibacterial with known sulphonamides drugs. Some of the later uses are as antitumor and anti-inflammatory agents, pesticides, dyes, lubricants and analytical reagents. 1, 3, 4-Thiadiazole and its derivatives possess wide range of therapeutic activities like anticonvulsant[I], herbicidal[II], pesticidal[III], amoebicidal[IV], CNS depressant[V], antibacterial [VI-VII], antiviral [VIII]. In continuation of our work on benzo[b]thiophene nucleus [IX], it was contemplated to synthesize some new 1, 3, 4-thiadiazoles derivatives bearing benzo[b]thiophene moiety.

Substituted Oxazole derivatives are found to be associated with various biological activities such as antibacterial[X], antifungal [XI], antitubercular [XII], anti-inflammatory[XIII]. Oxazoles are well known as important structural units in a wide variety of biologically active natural products as well as useful synthetic intermediates [XIV-XVI]. Other applications of Oxazole derivatives include the use as pesticides, fluorescent whitening agents, lubricants, dyes and pigments[XVII-XX].

Results and Discussion:

The starting material 4-substitutedbenzylidene-2-phenyloxazol-5-one **(2)**, was synthesized by reported procedure [XXI], which on treated with Thiocarbohydrazide, in presence of catalytic amount of conc. Sulphuric acid in equal proportion, to form **(4)**, which reacted with acetic anhydride and sodium acetate, to get target molecule **(4).**

Scheme I


(1)
Sodium acetate
(Acetic anhydride).
(2)
Thiocarbohydrazide
(3)
Sodium acetate
(Acetic anhydride).
(4)

Spectral Data of 2-N-acetyl hydrazino,4-acetyl,7-phenyl,9-(4-methoxy benzylidene),1-thia,3,4,8,triaza,6-oxa Spiro[4.4] nona-2,7-diene (4a)

Yield: 81 %; m.p. =152-153°C: IR (cm^{-1}): 1690 (C=O), 2258 (C=N), 3315 (NH)**,**
^{1}H NMR(DMSO-d_6,δ/ ppm): 2.82 (s,3H, CH_3), 2.58 (s,3H, CH_3), 3.28 (s,3H, OCH_3),4.16 (s,1H, CH), 7.24-8.03 (m, 9H, Ar- H), 8.74 (s, 1H, NH), 9.06 (s,1H,NH),
^{13}C NMR(DMSO-d_6,δ/ ppm): 21.45 (CH_3), 29.67 (CH_3), 59.46 (C), 126.46-141.90 (C=C,Ar-C),164.51 (C=N), 165.19 (C=N) 187.44 (C=O) 188.10 (C=O) .Anal.Calcd for $C_{22}H_{21}N_5O_4S$: C,58.53;H,4.65;N,15.52%.Found: C,58.48;H,4.62,N,15.44%.

Spectral Data of 2-N-acetyl hydrazino,4-acetyl,7-phenyl,9-(4-hydroxy benzylidene),1-thia,3,4,8-triaza,6-oxa Spiro[4.4] nona-2,7-diene (4b)

Yield:84 %; m.p.=123-125°C: IR (cm^{-1}): 1715 (C=O), 2273 (C=N), 3290 (OH)**,** 3343 (NH)**,**
^{1}H NMR(DMSO-d_6,δ/ ppm): 2.18 (s,3H, CH_3), 2.35 (s,3H, CH_3), 4.05 (s,1H, CH), 5.32 (s,1H, OH), 7.24-8.03 (m,9H, Ar- H), 8.73 (s,1H,NH), 9.21 (s, 1H, NH),
^{13}C NMR(DMSO-d_6,δ/ ppm): 24.56 (CH_3), 28.35 (CH_3), 58.56 (C), 129.46-140.90 (C=C,Ar-C),160.28 (C=N), 164.09 (C=N) 186.11 (C=O) 189.30 (C=O) . Anal.Calcd for $C_{21}H_{19}N_5O_4S$: C,57.66;H,4.34;N,16.01%.Found: C,57.61;H,4.32,N,15.92%.

Spectral Data of 2-N-acetyl hydrazino,4-acetyl,7-phenyl,9-(4-hydroxy 3-methoxy benzylidene),1-thia,3,4,8,triaza,6-oxa Spiro[4.4] nona-2,7-diene (4c)

Yield:84 %; m.p.=152-153°C: IR (cm^{-1}): 1690 (C=O), 2258 (C=N), 3390 (OH)**,** 3315 (NH)**,**
^{1}H NMR(DMSO-d_6,δ/ ppm): 2.82 (s,3H, CH_3), 2.58 (s,3H, CH_3), 3.28 (s,3H, OCH_3),4.16 (s,1H, CH), 5.42 (s,1H, OH), 7.24-8.03 (m,8H, Ar- H), 8.68 (s, 1H, NH), 9.06 (s,1H,NH),
^{13}C NMR(DMSO-d_6,δ/ ppm): 21.45 (CH_3), 29.67 (CH_3), 59.46 (C), 126.46-141.90 (C=C,Ar-C),164.51 (C=N), 165.19 (C=N) 187.44 (C=O) 188.10 (C=O) .Anal.Calcd for $C_{22}H_{22}N_5O_5S$: C,56.41;H,4.70;N,14.95%.Found: C,56.35;H,4.62,N,14.86%.

Spectral Data of 2-N-acetyl hydrazino,4-acetyl,7-phenyl,9-(4-Cholro benzylidene),1-thia,3,4,8,triaza,6-oxa Spiro[4.4] nona-2,7-diene (4d)

Yield: 64 %; m.p.=129-130°C: IR (cm^{-1}): 1745 (C=O), 2212 (C=N)**,** 3389 (NH)**,**
^{1}H NMR(DMSO-d_6,δ/ ppm): 2.48 (s,3H, CH_3), 2.10 (s,3H, CH_3), 4.21 (s,1H, CH), 7.57-8.54 (m,9H, Ar- H), 8.81 (s, 1H, NH), 9.12 (s,1H,NH),
^{13}C NMR(DMSO-d_6,δ/ ppm): 25.69 (CH_3), 28.77 (CH_3), 62.51 (C), 127.86-140.73 (C=C,Ar-C),161.64 (C=N), 153.17 (C=N) 181.24 (C=O) 185.13 (C=O) .Anal.Calcd for $C_{21}H_{18}N_5O_3SCl$: C,55.32;H,3.95;N,15.36%.Found: C,55.29;H,3.86,N,15.29%.

Spectral Data of 2-N-acetyl hydrazino,4-acetyl,7-phenyl,9-benzylidene,1-thia,3,4,8,triaza,6-oxa Spiro[4.4] nona-2,7-diene (4e)

Yield: 73 %; m.p.=134-135°C: IR (cm^{-1}): 1715 (C=O), 2276 (C=N)**,** 3269 (NH)**,**
^{1}H NMR(DMSO-d_6,δ/ ppm): 2.50 (s,3H, CH_3), 2.28 (s,3H, CH_3), 5.19 (s,1H, CH), 6.96-8.31(m,10H, Ar- H), 8.71 (s,1H,NH), 9.18 (s, 1H, NH),
^{13}C NMR(DMSO-d_6,δ/ ppm): 25.69 (CH_3), 28.77 (CH_3), 62.51 (C), 127.86-140.73 (C=C,Ar-C),161.64 (C=N), 153.17 (C=N) 181.24 (C=O) 185.13 (C=O) .Anal.Calcd for $C_{21}H_{19}N_5O_3S$: C,59.85;H,4.51;N,16.62%.Found: C,59.81;H,4.45,N,16.54%.

Spectral Data of 2-N-acetyl hydrazino,4-acetyl,7-phenyl,9-(2-hydroxy benzylidene),1-thia,3,4,8,triaza,6-oxa Spiro[4.4] nona-2,7-diene (4f)

Yield: 69 %; m.p.=112-114°C: IR (cm^{-1}): 1695 (C=O), 2371 (C=N), 3312 (OH), 3375 (NH), ^{1}H NMR (DMSO-d_6,δ/ ppm): 2.20 (s,3H, CH_3), 2.15 (s,3H, CH_3), 4.25 (s,1H, CH), 5.82 (s,1H, OH), 7.34-8.56 (m,9H, Ar- H), 8.78 (s,1H,NH), 9.21 (s, 1H, NH), ^{13}C NMR(DMSO-d_6,δ/ ppm): 24.56 (CH_3), 28.35 (CH_3), 58.56 (C), 129.46-140.90 (C=C, Ar-C),160.28 (C=N), 164.09 (C=N) 186.11 (C=O) 189.30 (C=O) .Anal.Calcd for $C_{21}H_{19}N_5O_4S$: C,59.66;H,4.34;N,16.01%.Found: C,59.58;H,4.29,N,15.95%.

Experimental:

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Table I: Physical data of Compounds 3 & 4

Compounds	R	m.p. (°C)	Yield (%)
3a	-OCH_3	168-170	78
3b	4-OH	156-158	74
3c	4-OH, 3-OCH_3	185-187	82
3d	4-Cl	176-178	76
3e	-H	156-158	62
3f	2-OH	145-147	61
4a	4-OCH_3	152-153	81
4b	4-OH	123-125	84
4c	4-OH, 3-OCH_3	152-153	84
4d	4-Cl	129-130	64
4e	-H	134-135	73
4f	2-OH	112-114	69

General Procedure:

Synthesis of 4-(substitutedbenzylidene)-2-phynyloxazole-5(4H)-ylidene) thiocarbono-hydrazide (3)

An equimolar mixture of (**2**) (0.01 mol) and Thiocarbohydrazide (1.06 gms, 0.01 mol) were refluxed in alcohol (20 ml) as a solvent and Conc. H_2SO_4 (0.5 ml) as a catalyst. The progress of the reaction was monitored on TLC. Upon Completion, the reaction was quenched onto crushed ice. The separated solid was filtered, washed with cold water and crystallized from alcohol, to yield (**3**).

Synthesis of 2-N-acetyl hydrazino,4-acetyl,7-phenyl,9-(substitutedbenzylidine),1-thia, 3,4,8,triaza,6-oxa Spiro[4.4] nona-2,7-diene (4)

A mixture of **(3)** (0.01 mol), acetic anhydride (15 ml) and sodium acetate (0.02 mol) were stirred at 10-15°C for 30 mins. Then the content was stirred at 65-70°C for 1 hr. the progress of the reaction was monitored on TLC. Upon completion, the content was poured into cold water. Solid thus obtained was filtered, washed with cold water and purified by column chromatography, to get targeted **(4)** (Solvent System = n-Hexane: Ethyl acetate = 8:2)

Antimicrobial activities:

All the compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method [21, 22]. The zone of inhibition was measured in mm and the activity was compared with standard drug. The data is given in **TABLE II**.

Table II

Antibacterial Activity of compound 3 & 4				
Comp.	**Zone of inhibition (in mm)**			
	Gram Positive		**Gram negative**	
	S.aureus	**C.diphtheria**	**P.aeruginosa**	**E.coli**
3b	22	20	21	19
3c	21	18	20	18
3d	18	19	18	14
3e	16	18	17	18
4b	21	22	16	17
4c	20	21	18	15
4d	18	19	21	14
4e	17	21	21	16
Ampycilin trihydrate	26	28	24	21
DMSO	0	0	0	0

* Diameter of the disc was 6mm;
Concentration of the compounds taken was about 100 µg/mL.

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