Asian Journal of Chemistry Vol. 8, No. 3 (1996), 529–535

Synthesis and Studies on the Biological Activity of Some New Spiro Heterocyclic Compounds

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A series of some spiro compounds covering thiazolidinones, β-lactams and triazolidine incorporating 3-methyl-1-phenyl(4,5-b)-furan-5-one (III_{a-d}, IV_{a-d} and V_{a-d}) were prepared. The synthesis was proceeded through cycloaddition reaction of thioglycolic acid, monochloroacetyl chloride and diazomethane to the newly reported 3-methyl-1-phenyl-(4,5-b)-3-aryl(naphthyl)imino furan-5-one (II_{a-d}). The biological screening of some selected spiro compounds was tested against some bacterial and fungal strains.

INTRODUCTION

Our interest in the synthesis of new systems having potential antibacterial activity[1–5] prompted us to explore the possibility of utilizing some Schiff bases[6–8] as substrated for the synthesis of new thiazolidine, β-lactam and triazolidine derivatives. This sort of compounds are known to be of special value in medicinal chemistry[9–11]

RESULTS AND DISCUSSION

The starting compound 3-methyl-1-phenyl(4,5-b)-furan-5-one (I) was prepared by 1,4-cyclocondensation reaction of 3-methyl-1-phenylpyrazol-5-one with monochloroacetyl chloride in the presence of triethylamine as catalyst and benzene as solvent (Scheme 1). The structure of (1) was confirmed by elemental analysis, IR and ^1H NMR spectral data (Tables 1, 2).

The condensation of I with equimolecular ratio of nitroso compounds such as *p*-nitrosophenol, *p*-nitroso-N-dimethylaniline, β-nitroso-α-naphthol and α-nitroso-β-naphthol in the presence of piperidine afforded 3-methyl-1-phenyl-(4,5-b)-3-aryl(naphthyl)imino-furan-5-one (II_{a-d}).

The structure of II_{a-d} was established by elemental analysis, IR and ^1H NMR spectral data (Tables 1, 2).

Cycloaddition of thioglycolic acid to the previously prepared aryl/naphthyl imino derivatives (II_{a-d}) proceeded smoothly in boiling benzene using a water separator for five days[12] to afford 3-methyl-1-phenyl pyrazolo(4,5-b)-furan-3-spiro(thiazolidino)-5-one derivatives (III_{a-d}) (Scheme 1).

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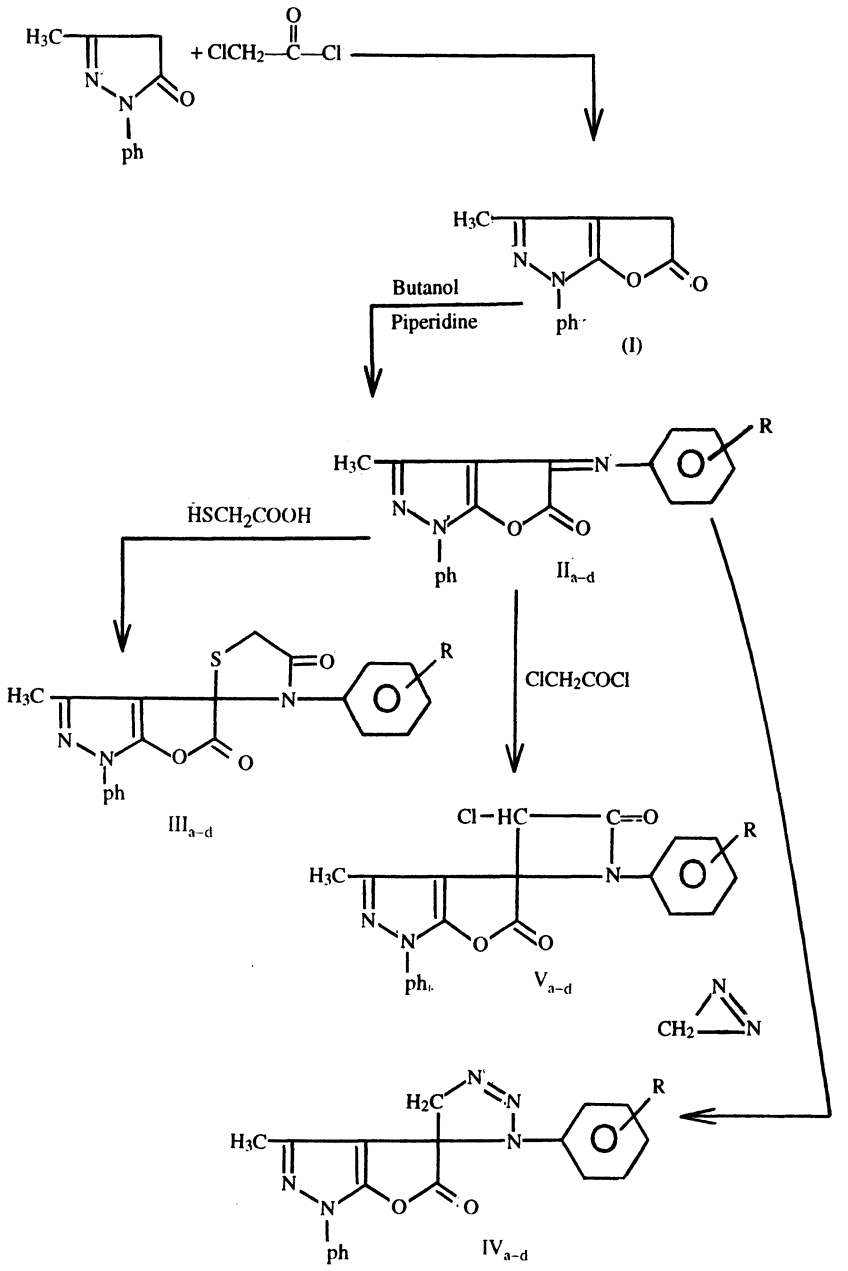

(II, III, IV, V) a, R = OH—4; b, R = $N(CH_3)_2$—4; c, R = 2—OH, 3,4-benzosubstituent; d, R = 2—OH, 5,6-benzosubstituent

The structure of III_{a-d} was proved by elemental analysis, IR and ^1H NMR spectral data (Tables 1, 2).

TABLE-1
CHARACTERISATION OF 3-METHYL-1-PHENYLPYRAZOL(4, 5-b)-FURAN-5-ONE (I), ITS ARYL(NAPHTHYL)-IMINO (II_{a-d}) DERIVATIVES AND THEIR SPIRO HETEROCYCLIC COMPOUNDS (III_{a-d}, IV_{a-d} AND V_{a-d})

Compound No.	m.p. (°C)	Yield (%)	Molecular formula (m.w.)	Elemental analysis % Found (Calcd.)		
				C	H	N
I	145	70	$C_{12}H_{10}N_2O_2$ (214)	67.35 (67.29)	4.71 (4.76)	13.05 (13.08)
II_a	169	65	$C_{18}H_{13}N_3O_3$ (319)	67.40 (67.71)	4.01 (4.08)	13.30 (13.17)
II_b	155	45	$C_{20}H_{18}N_4O_2$ (346)	69.50 (69.36)	5.10 (5.20)	16.30 (16.18)
II_c	180	60	$C_{22}H_{15}N_3O_3$ (369)	71.41 (71.54)	4.09 (4.07)	11.44 (11.38)
II_d	190	56	$C_{22}H_{15}N_3O_3$ (369)	71.60 (71.54)	4.00 (4.07)	11.50 (11.38)
III_a	160	45	$C_{20}H_{15}N_3O_4S$ (393)	61.09 (61.07)	3.92 (3.82)	10.80 (10.69)
III_b	185	40	$C_{22}H_{20}N_3O_3S$ (406)	65.06 (65.02)	4.98 (4.93)	10.50 (10.34)
III_c	220	35	$C_{24}H_{17}N_3O_4S$ (443)	65.20 (65.01)	3.90 (3.84)	9.60 (9.48)
III_d	195	38	$C_{24}H_{17}N_3O_4S$ (443)	65.34 (65.01)	3.60 (3.84)	9.52 (9.48)
IV_a	260	53	$C_{20}H_{14}N_3O_4Cl$ (395.5)	60.82 (60.68)	3.74 (3.54)	10.20 (10.62)
IV_b	210	42	$C_{22}H_{19}N_4O_3Cl$ (422.5)	62.69 (62.49)	4.61 (4.50)	13.30 (13.25)
IV_c	195	38	$C_{24}H_{16}N_3O_4Cl$ (445.5)	64.71 (64.65)	3.62 (3.59)	9.50 (9.43)
IV_d	230	27	$C_{24}H_{16}N_3O_4Cl$ (445.5)	64.55 (64.65)	3.47 (3.59)	9.48 (9.43)
V_a	230	33	$C_{19}H_{15}N_5O_3$ (361)	63.49 (63.16)	4.13 (4.16)	19.40 (19.39)
V_b	205	28	$C_{21}H_{20}N_6O_2$ (388)	65.10 (64.95)	5.18 (5.15)	21.70 (21.65)
V_c	240	30	$C_{23}H_{17}N_5O_3$ (411)	67.19 (67.15)	4.18 (4.14)	17.07 (17.03)
V_d	280	35	$C_{23}H_{17}N_5O_3$ (411)	67.20 (67.15)	4.22 (4.14)	17.10 (17.03)

The reaction of (II_{a-d}) with equimolecular ratio of monochloroacetyl chloride in the presence of triethylamine as catalyst and dioxane as solvent afforded the

corresponding 3-methyl-1-phenyl pyrazolo(4,5-b) furan-3-spiro-β-lactam-5-one derivatives (IV_{a-d}).

TABLE-2

IR and ^1H NMR spectral data of the starting compound 3-methyl-1-phenyl(4,5-b) furan-5-one and some selected spiro heterocyclic compounds

Compound No.	IR (ν_{max}(KBr) cm^{-1})	^1H NMR (DMSO) ppm
I	1730 (C=O)	1.9 (s, 3H, (CH_3)), 1.2 (s, 2H, (CH_2)), 7.2–7.9 (m, 5H, aromatic)
II_c	1590 (C=N) 1735 (C=O) 3500–3300 (OH)	7.8–8.7 (m, 11H, aromatic), 4.2–5.6 (s, 1H, OH), 1.8 (s, 3H, (CH_3))
III_c	3340 (OH) 2930–2870 (CH stretching) 1735 (C=O)	7.9–8.7 (m, 11H aromatic), 4.3–5.5 (s, 1H, OH), 1.9 (s, 3H, (CH_3)), 1.4–2.3 (s, 2H, CH_2 thiazolidinone)
IV_c	1735 (C=O) 1240 (C—N)	7.8–8.7 (m, 12H, aromatic), 4.3–5.2 (s, 1H, OH), 1.9 (s, 3H, (CH_3))
V_c	1735 (C=O) 1530 (N=N) 1330 (C—N)	7.9–8.7 (m, 11H, aromatic), 4.2–5.1 (s, 1H, OH), 1.9 (s, 3H, (CH_3)), 5.6 (s, 2H, triazoline ring)

The structure of IV_{a-d} was confirmed by elemental analysis, IR and ^1H NMR spectral data (Tables 1, 2).

The 1,3-cycloaddition reaction of diazomethane to the previously prepared imino derivatives (II_{a-d}) afforded the corresponding 3-methyl-1-phenyl-pyrazolo (4,5-b)-furan-3-spiro(triazoline)-5-one (V_{a-d}). The reaction was accomplished easily when an ethereal solution of diazomethane was added to a solution of imino derivatives (II_{a-d}) in absolute ethanol, and left in the refrigerator for 15 days to produce the desired triazoline compounds (V_{a-d}).

The structure of V_{a-d} was confirmed by elemental analysis and IR spectra which showed absorption bands at 1650 cm^{-1} and 1400 cm^{-1} due to ν(N—N) and ν(C—N) respectively[13].

The antibacterial and antifungal activities of some selected spiro heterocyclic compounds (II_{a-d}, III_{a-d}, IV_{a-d}, V_{a-d}) were determined using the filter paper discs method[14]. Thus samples of II, III, IV and V were dissolved in ethylene glycol, then transferred to the filter paper disc and the antibacterial activity was determined against *Bacillus stearetherophil* and *Serratia* and the fungal activity against *Aspergillus* and *Penicillium* species (Table-3).

Structure-biological activity relationship of some spiro thiazolidinones, β-lactams and triazoline (III_{a-d}, IV_{a-d} and V_{a-d}) was demonstrated relative to the parent 3-methyl-1-phenylpyrazol(4,5-b)-aryl(naphthyl)imino-furan-5-one (II_{a-d}). Thus the parent compounds II_{a-d} are less active, especially those having the 1-naphthoyl

TABLE-3
BIOLOGICAL SCREENING OF 3-METHYL-1-PHENYLPYRAZOLO(4,5-b) 3-ARYL(NAPHTHYL) IMINO FURAN-5-ONE II_{a-d} AND THEIR SPIRO HETEROCYCLIC COMPOUNDS (III_{a-d}, IV_{a-d}, V_{a-d})

Organism used	Compound Tested															
	II				III				IV				V			
	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
A. BACTERIAL STRAINS: *Bacillus steareotherophile*	++	+++	–	++	+++	++++	++	+++	++++	+++	+++	++++	++	++	+	+
Serratia	+	++	–	+	++	+++	+	++	+++	++	++	+++	+	++	++	+
B. FUNGAL STRAINS: *Asperigillus niger*	++	+	–	+	++	++	+	++	+++	++	++	+++	++	+	–	+
Penicillum cyclopium	+	+++	+	++	++	+++	+	++	++++	+	++	++	+	+	—	++

(++++, +++) High potency, (++) Medium potency, (+) Lower potency, (–) No potency.

moiety (II_c). The imino derivatives $II_{a, b, d}$ are slightly more biologically active than those of II_b. Insertion of spiro thiazolidinone br β-lactams and/or thiazoline to the parent aryl(naphthyl)imino derivatives (II_{a-d}) showed that high antibacterial activity was associated especially with the compounds containing β-lactam rings.

The same observations of antifungal activities for spiro heterocyclic ring system were noted; the potency was influenced by aryl and/or naphthoyl substituent (Table-3).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were determined with Perkin-Elmer infrared 127B spectrophotometer. The ^1H NMR spectra were determined with EM 390 90 MHz NMR spectrometer.

Synthesis of 3-methyl-1-phenylpyrazol(4,5-b)-furan-5-one (I)

A mixture of 3-methyl-1-phenylpyrazol-5-one (0.01 mol) and monochloroacetyl chloride (0.01 mol) in benzene 30 mL containing triethylamine (2–6 mL) was refluxed for 8 h. The reaction mixture was filtered, concentrated, and allowed to cool at room temperature whereby the product was separated, filtered off, washed several times with water, dried and crystallised from the proper solvent (*cf.* Table-1).

Synthesis of 3-methyl-1-phenylpyrazol(4,5-b)-3-aryl(naphthyl)imino-furan-5-one (II_{a-d})

A mixture of I (0.01 mol) and nitroso compounds (*p*-nitrosophenol, *p*-nitroso-N-dimethylaniline, β-nitroso-α-naphthol and α-nitroso-β-naphthol, 0.01 mol) in butanol 20 mL containing piperidine (1 mol) was refluxed for 10–14 h. The hot reaction mixture was filtered, concentrated and allowed to cool at room temperature for 3 days where the imino derivatives (II_{a-d}) precipitated out (Table-1).

Synthesis of 3-methyl-1-phenylpyrazolo(4,5-b)-furan-3-spiro-thiazolidino-5-one (III_{a-d})

A mixture of the imino derivatives (II_{a-d}, 0.01 mol) and mercapto-acetic acid (0.01 mol) in dry benzene was refluxed for 12–15 h. The hot reaction mixture was filtered, concentrated, and boiling water was added. The products (III_{a-d}) separated out and were filtered off, washed several times with water, dried and crystallised from the proper solvents (*cf.* Table-1).

Synthesis of 3-methyl-1-phenylpyrazol(4,5-b)-furan-spiro-3-β-lactams-5-one (IV_{a-d})

To a well-stirred solution of the imino derivatives (II_{a-d}, 0.01 mol) in dioxane 30 mL and 0.02 mol of triethylamine, monochloroacetyl chloride (0.02 mol) was added dropwise at room temperature. The reaction mixture was stirred for 9 h and left at room temperature for 3 days. The precipitate of triethylamine hydrochloride was filtered off and washed thoroughly with dioxane. The filtrate was concentrated, poured with vigorous stirring on ice-water mixture and left

aside for overnight at room temperature whereby the products IV_{a-d} separated. They were filtered off, washed several times with water, dried and crystallised from the proper solvents (*cf.* Table-1).

Synthesis of 3-methyl-1-phenylpyrazol(4,5-b) furan spiro-3-triazolino-5-one (V_{a-d})

A solution of the imino derivatives (II_{a-d}, 0.01 mol) in ethanol (30 mL) was mixed with an ethereal diazomethane solution (obtained by decomposition of nitrosomethyl urea (6 g) with aqueous KOH. The reaction mixture was left at 0–5°C for 10 days whereby the products V_{a-d} were precipitated; these were filtered off, washed with water several times, dried and crystallised from the proper solvents (*cf.* Table-1).

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(*Received:* 15 January 1996; *Accepted:* 20 February 1996) AJC-1085