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HETEROCYCLIC SYSTEMS CONTAINING BRIDGEHEAD NITROGEN ATOM: SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF *p*-BIS(*s*-TRIAZOLO[3,4-*b*][1,3,4]THIADIAZIN-3-YL)PHENYLENE AND *p*-BIS(*s*-TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOL-3-YL)PHENYLENE

JAG MOHAN, G. S. R. ANJANEYULU and PRATIMA VERMA
Department of Chemistry, Maharshi Dayanand University, Rohtak 124 001, India

IN continuation of our earlier studies on the synthesis of condensed biologically active triazole systems[1-3], we report in this paper the synthesis of some heterocyclic systems derived from *p*-bis(5-mercapto-4-amino-*s*-triazol-3-yl)phenylene (I) in order to explore the possibility of the synthesis of heterocyclic systems with appreciable biological activity.

Compound I was prepared in excellent yield by the reaction of terephthalic acid bis-hydrazide with CS_2 and hydrazine following the method of Reid and Heindel[4].

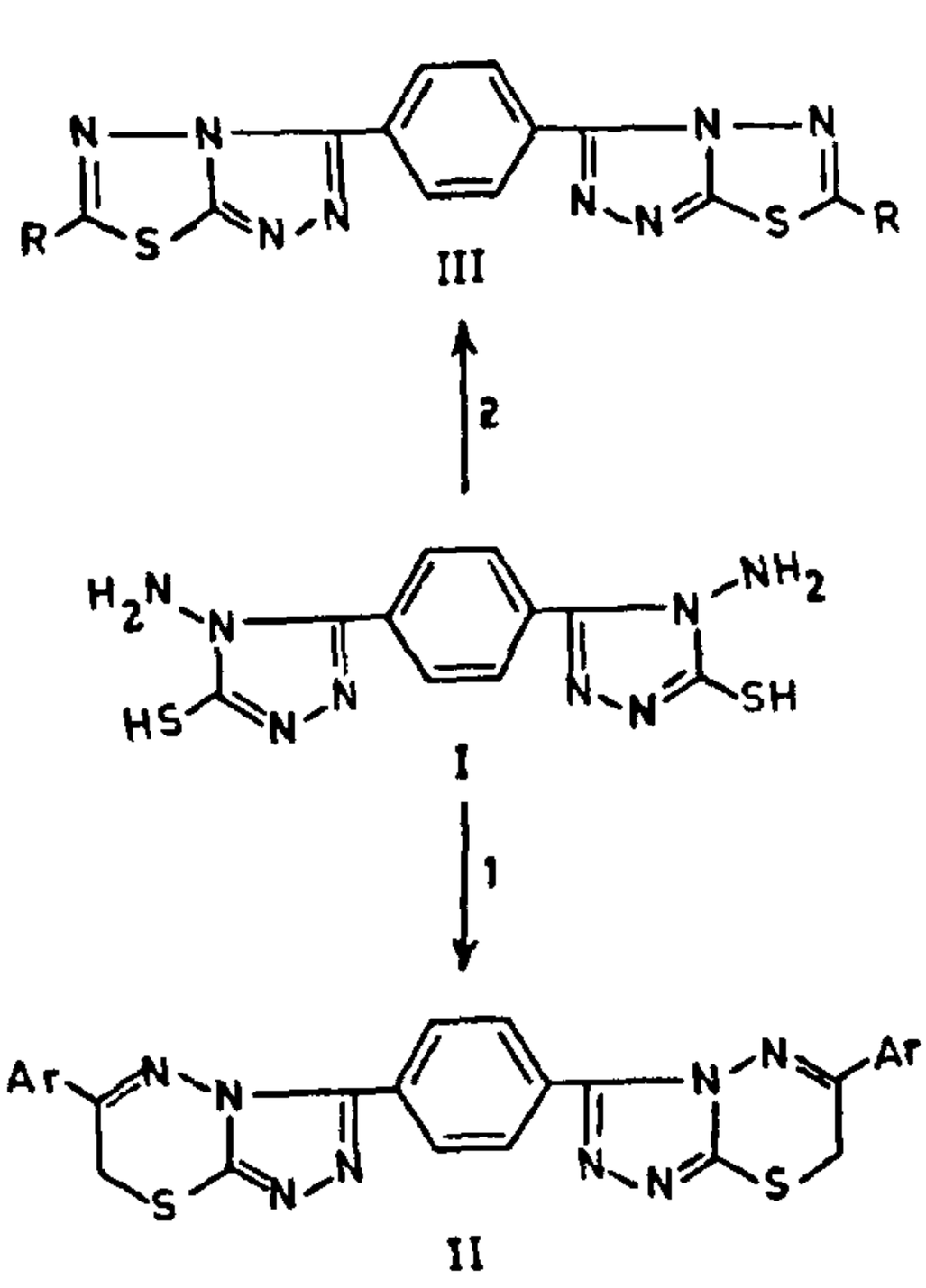
The reaction of I with α-haloketones and carboxylic acids in absolute ethanol yielded *p*-bis(7*H*-6-aryl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)phenylene (II) and *p*-bis(6-aryl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)phenylene (III) respectively in good yields.

The structures of II and III are compatible with their elemental analysis and spectroscopic data. The absence of C=O band in the IR spectra of compounds II and III corroborates the cyclic structures in these compounds.

Melting points reported are uncorrected. Thin-layer chromatography was performed on silica gel plates using acetone–benzene (2:3) as irrigant. IR spectra (ν_{max} cm^{-1}) in nujol were recorded on a Beckman IR-20 spectrometer.

p-Bis(5-mercapto-4-amino-s-triazol-3-yl)phenylene(I)

It was prepared from terephthalic acid bis-hydrazide following the method of Reid and Heindel[4], m.p. 280°C (d) (EtOH), yield 52%. Found: N, 36.85; S, 20.91. $C_{10}H_{10}N_8S_2$ requires N, 36.60; S, 20.92%. IR; 820 (*p*-disubstituted benzene ring), 1500 (C–N stretching), 1600 (C=C and C=N), 2600 (S–H stretching), 3020 (C–H stretching, aromatic), 3220, 3400 (N–H stretching, NH_2 group).



Scheme 1

p-Bis (7H-6-p-bromophenyl-s-triazolo [3,4-b] [1,3,4] thiadiazin-3-yl) phenylene (IIa, Ar = p-Br–C_6H_4–)

A mixture of I (1.53 g, 0.005 mol) and *p*-bromophenacyl bromide (2.78 g, 0.01 mol) in absolute ethanol (150 ml) was heated under reflux for 6 h. The salt separated was filtered and basified with ammonia solution. The solid thus obtained was filtered, washed with water and finally with hot ethyl alcohol; m.p. 225°C, yield 1.6 g (48.2%). Found: C, 47.23; H, 2.72; N, 16.43; S, 9.89. $C_{26}H_{16}N_8S_2Br_2$ requires C, 46.99; H, 2.41; N, 16.87; S, 9.64%. IR: 800 (1,4-disubstituted benzene ring), 1580, 1600 (C=C, C=N), 3060 (C–H stretching, aromatic).

The data for other *s*-triazolothiadiazines (II) prepared similarly are given in table 1.

p-Bis (6-p-chlorophenyl-s-triazolo [3,4-b] [1,3,4] thiadiazol-3-yl) phenylene (IIIa, R = p-Cl–C_6H_4–)

A mixture of I (1.53 g, 0.005 mol), *p*-chlorobenzoic acid (1.57 g, 0.01 mol) and $POCl_3$ (10 ml) was heated on a water bath for 1 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The resultant solid obtained was filtered, washed with water and crystallized from glacial acetic acid as yellow-coloured crystalline mass; m.p. 255°C, yield 1.7 g (62%). Found: C, 52.96; H, 2.46; N, 20.13; S, 11.35. $C_{24}H_{12}N_8S_2Cl_2$ requires C, 52.65; H, 2.19; N, 20.48; S, 11.70%. IR: 830 (1,4-disubstituted benzene), 1560, 1590 (C=C and C=N), 3050 (C–H stretching, aromatic).

The data for other *s*-triazolothiadiazoles (III) prepared similarly are given in table 2.

Antimicrobial activity

The compounds II (Ar = *p*-Br–C_6H_4–) and III (R = *p*-Cl–C_6H_4–) were tested for antimicrobial activity against *Staphylococcus aureus*, (a gram-positive bacterium), *Escherichia coli* and *Pseudomonas aeruginosa* (gram-negative bacteria) and *Candida albicans* (a fungus) by serial plate dilution method[5].

The minimum inhibitory concentration of compound III against *E. coli* and *S. aureus* was 125 μg/ml.

Compound II showed activity against *E. coli* and *S. aureus* when used undiluted and may be used for local application in the form of powder or ointment

Table 1 *Characterization data for s-triazolo thiadiazines (II)*

Ar	m.p. (°C)	Yield (%)	Mol. formula	Found (calc.) (%) C	H	N	S
p-Cl–C_6H_4–	198	52.2	$C_{26}H_{16}N_8S_2Cl_2$	54.62 (54.26)	2.41 (2.78)	19.86 (19.48)	11.53 (11.13)
p-NO_2–C_6H_4–	210(d)	61.6	$C_{26}H_{16}N_{10}S_2O_4$	52.75 (52.35)	2.28 (2.68)	— (—)	10.23 (10.74)
p-C_6H_5–C_6H_4–	176	63.9	$C_{38}H_{26}N_8S_2$	69.70 (69.30)	3.58 (3.95)	16.82 (17.02)	10.12 (9.73)

Table 2 *Characterization data for s-triazolo thiadiazoles (III)*

R	m.p. (°C)	Yield (%)	Mol. formula	Found (calc.) (%) C	H	N	S
C_6H_5–	200	56.5	$C_{24}H_{14}N_8S_2$	60.42 (60.25)	3.22 (2.93)	22.11 (22.43)	13.71 (13.39)
o-Cl–C_6H_4–	250	54.9	$C_{24}H_{12}N_8S_2Cl_2$	52.15 (52.65)	2.52 (2.19)	20.82 (20.48)	11.36 (11.70)
m-Cl–C_6H_4–	228	60.0	$C_{24}H_{12}N_8S_2Cl_2$	52.98 (52.65)	2.46 (2.19)	20.22 (20.48)	11.96 (11.70)
p-CH_3-C_6H_4–	220	53.0	$C_{26}H_{18}N_8S_2$	61.34 (61.66)	3.18 (3.56)	21.92 (22.12)	12.89 (12.65)
p-CH_3O C_6H_4-	235	66.9	$C_{26}H_{18}N_8S_2O_2$	58.34 (57.99)	3.83 (3.35)	20.61 (20.82)	11.56 (11.90)
2,4-Cl_2 C_6H_3-	228	58.0	$C_{24}H_{10}N_8S_2Cl_4$	46.32 (46.75)	1.94 (1.62)	18.58 (18.18)	9 89 (10.39)

provided further studies indicate absence of toxicity following local application.

11 November 1988

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SYNTHESIS AND CHARACTERIZATION OF SOME NEW 3-ACETYL-4-ARYL-2-PYRAZOLINES

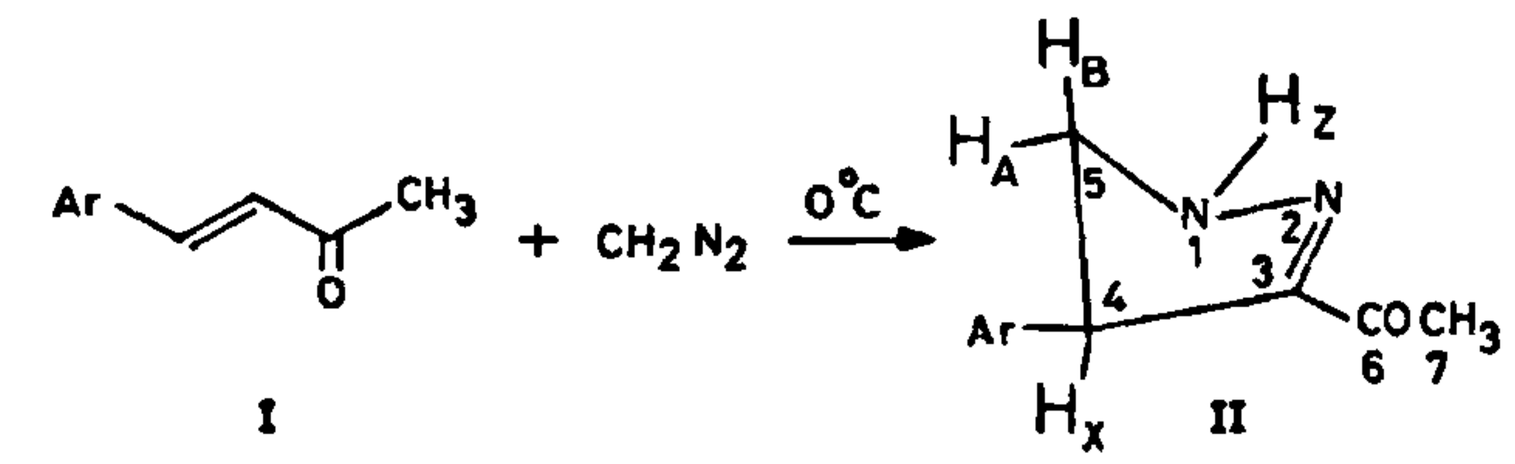
G. V. SUBBA RAJU and KOTHA S. RAO
Department of Chemistry, School of Mathematical and Physical Sciences, Sri Venkateswara University, Tirupati 517 502, India

SYNTHESIS of pyrazolines through cycloaddition of diazomethane to activated olefines has been known for a long time[1]. However, there is no general agreement on the structure of 2-pyrazolines[2–6]. Recently, we have established the structure of 3-aroyl-4-aryl-2-pyrazolines[7]. In continuation of this study, we report in this communication the synthesis and characterization of 3-acetyl-4-aryl-2-pyrazolines (IIa–h).

4-Aryl-3-buten-2-ones (Ia–h) were obtained by crossed aldol condensation of appropriately substituted aldehydes and acetone[8]. The ether solution of diazomethane prepared from nitrosomethylurea[9] was added to butenones (Ia–h) in ether at 0°C to give 3-acetyl-4-aryl-2-pyrazolines (IIa–h). In the case of Ia, the formation of 1-pyrazoline[1] was noticed, but this changed to 2-pyrazoline, IIa.

The IR data (table 1) for the pyrazolines (IIa–h) indicate bands in the regions 3280–3340, 1630–1650 and 1520–1530 cm^{-1} assigned to NH, C=O and C=N stretch vibrations respectively. It is significant to note that $\nu_{C=N}$ shifted to lower frequencies while $\nu_{C=O}$ shifted to higher frequencies compared to those of 3-aroyl-4-aryl-2-pyrazolines[5–7].

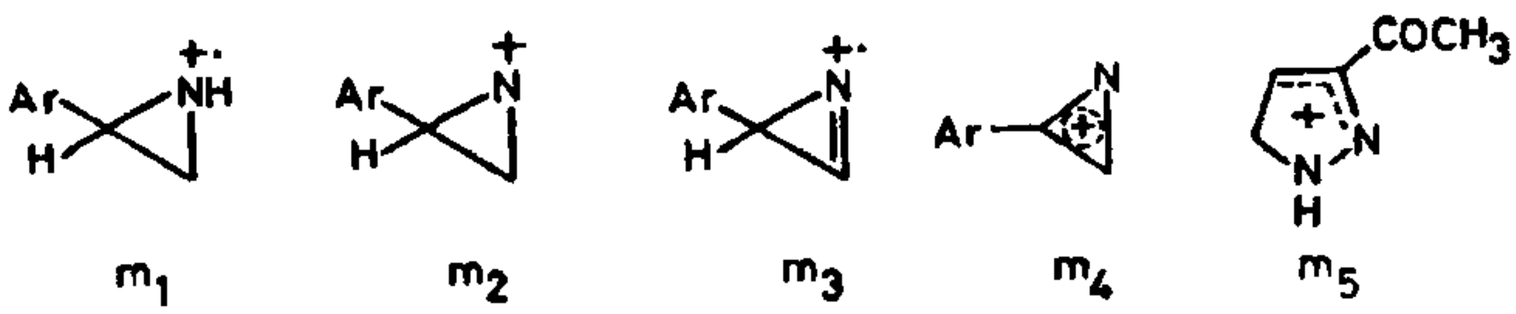
^{1}H NMR spectroscopic data (table 2) contain ABX pattern of signals attributed to 4-methine and 5-methylene protons. It is interesting to note that 200 MHz spectra clearly resolved the NH signal, whereas in 90 MHz spectra the signal could not be traced out. In case of IIb and IIc the coupling with NH proton is also discernible.



I II

Ar

(a) Phenyl
(b) 4-Methylphenyl
(c) 4-N, N-dimethylphenyl
(d) 2-Chlorophenyl
(e) 4-Chlorophenyl
(f) 3,4-Methylenedioxyphenyl
(g) 4-Methoxyphenyl
(h) Furan-2-yl



m_1 m_2 m_3 m_4 m_5