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HETEROCYCLIC SYSTEMS CONTAINING BRIDGEHEAD NITROGEN ATOM : SYNTHESIS AND ANTIMICROBIAL, ANTIFUNGAL ACTIVITY OF *cis*-8,8a-DIHYDROPYRAZOLO[3',4':4,5]THIAZOLO[2,3-*b*]-*s*-TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLE

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ABSTRACT

A synthesis of 9a-aryl-7,8-diaryl-3-(*p*-nitrophenyl)-*cis*-8,8a-dihydropyrazolo[3',4' :4,5]thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole **4** has been achieved. Condensation of 3-(*p*-nitrophenyl)-6-aryl-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole **1** with thioglycollic acid yield 8a-aryl-3-(*p*-nitrophenyl)-thiazolo [2, 3-*b*]-*s*-triazolo [3,4-*b*] [1,3,4]-thiadiazol-6(7*H*)-one **2.** The thiazolidinones **2** on reaction with *p*-chlorobenzaldehyde yield 7-*p*-chlorobenzylidene-8a-aryl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-s-triazolo[3,4-*b*][1,3,4]-thiadiazol-6(7*H*)-one **3.** Condensation of **3** with 2, 4- dinitrophenylhydrazine hydrate furnish **4.** The antibacterial and antifungal activity of some of the compounds have also been evaluated.

KEYWORDS

9a-aryl-7,8-diaryl-3-(*p*-nitrophenyl)-*cis*-8,8a-dihydropyrazolo[3',4':4,5]thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole ; 3-(*p*-nitrophenyl)-6-aryl-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole **;** 8a-aryl-3-(*p*-nitrophenyl)-thiazolo [2 , 3-*b*]-*s*-triazolo [3 ,4-*b*] [1,3, 4]-thiadiazol-6 (7*H*)-one ; 7-*p*-chlorobenzylidene-8a-aryl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-s-triazolo[3,4-*b*][1,3,4]-thiadiazol-6(7*H*)-one; antibacterial and antifungal activity

INTRODUCTION

In continuation of our earlier work on the synthesis of novel bridgehead nitrogen heterocyclic systems[i-viii] the author reports herein the synthesis of pyrazolo[3',4': 4,5]thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole system.

3-(*p*-nitrophenyl)-6-(*p*-chlorophenyl)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole **1A**, obtained by the condensation of 3-(*p*-nitrophenyl)-4-amino-5-mercapto-*s*-triazole with *p*-chlorobenzoic acid, on condensation with thioglycollic acid afforded 8a-*p*-chlorophenyl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-*s*-triazolo [3,4-*b*][1,3,4]thiadiazol-6(7*H*)-one **2A.** Condensation of **2A** with *p*-chlorobenzaldehyde yielded 7-*p*-chlorobenzylidene-8a-*p*-chlorophenyl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazol-6-(7*H*)-ones **3A.** The structures **2A** and **3A** were supported by their IR spectra. The parent thiazolidinone showed a peak at 1720cm^{-1} (>N-C=O) but the exocyclic double bond at 7-position being in conjugation with the carbonyl group at 6-position produced a bathochromic shift[ix] in the carbonyl absorption of **3A**. The band appeared at 1700cm^{-1} in **3A** (Ar=*p*-Cl-C_6H_4). Condensation of **3A** with 2,4-dinitrophenylhydrazine yielded the cyclized products, 9a-aryl-7, 8-diaryl-3-(*p*-nitrophenyl)-*cis*-8,8a-dihydropyrazolo[3',4':4,5] thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles **4A**. The structures of **4** were supported by their ^{1}H NMR spectral data (vide Experimental). The appearance of two doublets at δ 7.83 & 7.95 (J=10.0 Hz) respectively for the protons 8a and 8 corroborated the cyclic structure and *cis* configuration[x].

ANTIMICROBIAL ACTIVITY

The compounds **2** and **4** were evaluated for their antimicrobial activity against the gram-positive *Staphylococcus aureus,* gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* and the fungus *Candida albicans.* Neat samples and serial plate dilution method were used[xii].

The minimum inhibitory concentration (MIC) of the compounds **2** and **4** against *P. aeruginosa* and *S. aureus* were found to be 250 μg/ml and 500 μg/ml respectively. These compounds were also found to be active against *C. albicans,* when tested as neat samples.

EXPERIMENTAL AND RESULTS

TLC was run on silica gel G plates using acetone-benzene (1:3) as irrigant. Melting points are uncorrected. IR (KBr)(cm^{-1}) and ^{1}H NMR ($CDCl_3$) (δ ppm downfield from TMS) spectra were recorded on a Hitachi-215 and Varian VXR-200 MHz spectrometers respectively. C, H and N analyses were carried out on a Yanaco MT-3 (Japan) analyser.

3-(*p*-nitrophenyl)-6-*p*-chlorophenyl-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole 1A

A mixture of 4-amino-5-mercapto-3-(*p*-nitrophenyl)-*s*-triazole (5.0g, 0.02mole) and *p*-chlorobenzoic acid (3.2g, 0.02mole) in $POCl_3$ (20ml) was heated under reflux in an oil bath at 120°C for one hour. The reaction mixture was cooled, poured into ice and neutralized with aq. K_2CO_3 solution. The solid thus separated was filtered, washed thoroughly with water and recrystallized from gl. acetic acid, yield 3.0g (39.78%), m.p.>250°C. (Found: C, 50.63; H, 2.48; N, 19.23; S, 8.76. $C_{15}H_8N_5SO_2Cl$ requires C, 50.34; H, 2.23; N, 19.58; S, 8.95%); IR: 830, 840 (1, 4-disubstituted benzene ring), 1355, 1535 (Nitro group), 1525 (C-N stretching), 1610, 1625 (C=C & C = N), 3040 (aromatic C-H stretching).

A similar method was adopted for the synthesis of compound 3-(*p*-nitrophenyl)-6-*p*-nitrophenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole **1B** (Ar=*p*-O_2N-C_6H_4) having m.p. 230°C, yield 3.0g(38.65%). (Found: C,48.71; H,2.47; N, 22.67; S, 8.43. $C_{15}H_8N_6SO_4$ requires C, 48.91; H, 2.17; N, 22.80; S, 8.69%); IR: 820, 840 (1,4-disubstituted benzene ring), 1345, 1540 (NO_2 group), 1525 (C-N stretching), 1600, 1620 (C = C and C = N), 3050 (aromatic C-H stretching).

Also 3-(*p*-nitrophenyl)-6-*m*-chlorophenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole **1C** (Ar=*m*-Cl-C_6H_4) was

prepared having m.p. 200°C, yield 2.9g (38.46%) (Found : C, 50.67; H, 2.52; N, 19.32; S, 8.67. $C_{15}H_8N_5SO_2Cl$ requires C, 50.34; H, 2.23; N, 19.58; S, 8.95%); IR : 770, 840, 880 (1,3 and 1,4-disubstituted benzene ring), 1350, 1530 (Nitro group), 1515 (C - N stretching), 1620 (C = C and C = N), 3040 (aromatic C-H stretching).

8a-*p*-chlorophenyl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazol-6(7*H*)-one 2A

A mixture of 1A (3.0g, .008mole), thioglycollic acid(0.77g, .008mole) in dry toluene (40ml) was heated under reflux using Dean-Stark water separator for 10-12 hr, concentrated & cooled. The solid thus separated was filtered, washed with water and crystallized from gl acetic acid, m.p. 115°C, yield (27.70%). (Found : C, 47.62; H, 2.33; N, 16.48; S, 14.52. $C_{17}H_9N_5S_2ClO_3$ requires C, 47.38; H, 2.09; N, 16.26; S, 14.86%); IR : 835, 845 (1,4-disubstituted benzene ring), 1520 (C - N stretching), 1600, 1620 (C = C & C = N), 1715 (C = O), 3040, 3060 (aromatic C-H stretching).

A similar method was adopted for the synthesis of compound 8a-*p*-nitrophenyl-3-(*p*-nitrophenyl)-thiazolo [2, 3-*b*]-*s*-triazolo [3, 4-*b*] [1,3,4]thiadiazol-6(7*H*)-one **2B**(Ar=*p*-O_2N-C_6H_4) having m.p. 220°C, yield 1.5g (41.66%). (Found: C, 46.37; H, 2.42; N, 18.89; S, 14.26. $C_{17}H_{10}N_6O_5S_2$ requires C, 46.15; H, 2.26; N, 19.00; S, 14.47%); IR : 830, 840 (1,4-disubstituted benzene ring), 1515 (C-N stretching), 1610,1625 (C = C and C = N), 1720 (C = O), 3050 (aromatic C - H stretching).

Also 8a-*m*-chlorophenyl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazol-6(7*H*)-one **2C** (Ar=*m*-Cl-C_6H_4) was prepared having m.p. 195°C, yield 1.0g(27.70%). (Found : C, 47.56; H, 2.29; N, 16.47; S, 14.63. $C_{17}H_9N_5S_2ClO_3$ requires C, 47.38; H, 2.09; N, 16.26; S, 14.86%); IR : 710, 775, 835, 875 (1,3 and 1,4-disubstituted benzene ring), 1520 (C-N stretching), 1355, 1535 (NO_2 group), 1600, 1620 (C = C and C = N), 1715 (C = O), 3040 (aromatic C - H stretching).

7-*p*-chlorobenzylidene-8a-*p*-chlorophenyl-3-(*p*-nitrophenyl)thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazol-6(7*H*)-ones $3A_1$

A mixture of **2A**(1.5g, .002mole), *p*-chlorobenzaldehyde (0.39g, .002mole), anhyd. sodium acetate (0.22g, .002mole) in gl acetic acid (30ml) was heated under reflux for 5 hr, concentrated, cooled and poured into crushed ice. The solid thus separated was filtered, washed with water and crystallized from glacial acetic acid, yield 1.0g(51.81%), m.p. 220°C. (Found : C, 51.73; H, 2.61; N, 12.39; S, 11.37. $C_{24}H_{13}N_5S_2Cl_2O_3$ requires C, 51.98; H, 2.34; N, 12.63; S, 11.55%); IR: 825, 840 (1,4-disubstituted benzene ring), 1360, 1530 (NO_2 group), 1600, 1630 (C=C and C = N), 1515 (C-N stretching), 1690 (C=O), 3040 (aromatic C-H stretching).

Similar method was adopted for the synthesis of compounds **$3A_2$, $3B_1$, $3B_2$, $3C_1$& $3C_2$**. Their characterization data is given in Table-1.

9a-(*p*-chlorophenyl)-7-(2",4"-dinitrophenyl)-8-(*p*-chlorophenyl)-3-(*p*-nitrophenyl)-*cis*-8,8a-dihydropyrazolo[3',4':4,5]thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles $4a_1$

A mixture of **$3A_1$**, (.400g, .0007mole), 2,4-dinitrophenylhydrazine (0.142g, .0007mole), anhydrous sodium acetate (.036g, .0007mole) in gl acetic acid (30ml) was heated under reflux for 6 hr. The reaction mixture was half concentrated, cooled. The solid thus separated was filtered and recrystallized from gl acetic acid, yield .200g (37.80%), m.p. 195°C. (Found : C, 49.31; H, 2.59; N, 17.37; S, 8.52. $C_{30}H_{17}N_9S_2O_6Cl_2$ requires C, 49.04; H, 2.31; N, 17.16; S, 8.71%); IR : 830, 840, 885 (1, 4-disubstituted and 1, 2, 4-trisubstituted benzene ring), 1355, 1530 (NO_2 group), 1530 (C-N stretching), 1610, 1630 (C = C & C = N), 3060 (aromatic

C-H stretching); ^{1}H NMR(DMSO) : 7.83(1H,d(J=10.0 Hz), C-8a-H), 7.95(1H,d(J=10.0 Hz), C-8-H), 7.60-8.37 (15H, m, aromatic protons).

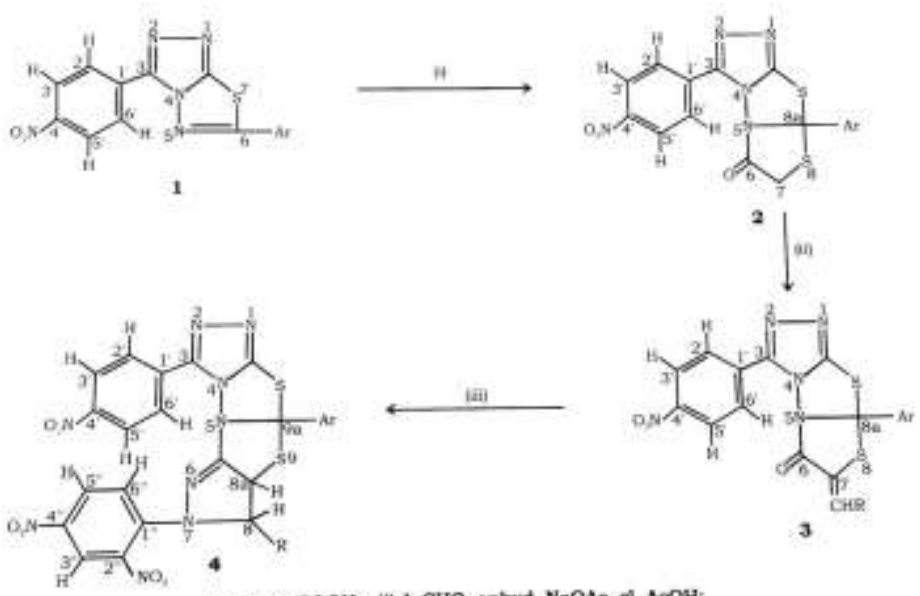
A similar method was adopted for the synthesis of compds **$4a_2$, $4b_1$, $4b_2$, $4c_1$,** & **$4c_2$** respectively, their characterization data is given in Table-2.

TABLE-1 Characterization data of compounds $3A_2$, $3B_1$, $3B_2$, $3C_1$, & $3C_2$

Compd.	Ar	R	m.p. °C	Yield %	Mol. Formula	Found (%)/Calcd.			
						C	H	N	S
$3A_2$	*p*-Cl-C_6H_4	*p*-H_3CO-C_6H_4	250	58.82	$C_{25}H_{16}N_5S_2ClO_4$	54.31 (54.59	2.73 2.91	12.92 12.73	11.37 11.64)
$3B_1$	*p*-O_2N-C_6H_4	*p*-Cl-C_6H_4	240	39.37	$C_{24}H_{13}N_6S_2ClO_5$	51.47 (51.20	2.09 2.31	14.69 14.93	11.56 11.37)
$3B_2$	*p*-O_2N-C_6H_4	*p*-H_3CO-C_6H_4	220	39.68	$C_{25}H_{16}N_6S_2O_6$	53.49 (53.76	2.61 2.86	15.31 15.05	11.67 11.46)
$3C_1$	*m*-Cl-C_6H_4	*p*-Cl-C_6H_4	200	46.63	$C_{24}H_{13}N_5S_2Cl_2O_3$	51.73 (51.98	2.58 2.34	12.39 12.63	11.29 11.55)
$3C_2$	*m*-Cl-C_6H_4	*p*-H_3CO-C_6H_4	195	52.28	$C_{25}H_{16}N_5S_2ClO_4$	54.38 (54.59	2.76 2.91	12.94 12.73	11.34 11.64)

TABLE-2 Characterization data of compounds $4a_2$, $4b_1$, $4b_2$, $4c_1$, & $4c_2$

Compd.	Ar	R	m.p. °C	Yield %	Mol. Formula	Found (%)/Calcd.			
						C	H	N	S
$4a_2$	*p*-Cl-C_6H_4	*p*-H_3CO-C_6H_4	210	37.76	$C_{31}H_{19}N_9S_2ClO_7$	49.63 (49.39	2.83 2.69	17.68 17.88	9.31 9.08)
$4b_1$	*p*-O_2N-C_6H_4	*p*-Cl-C_6H_4	200	37.87	$C_{30}H_{16}N_{10}S_2ClO_8$	48.19 (48.41	2.40 2.15	18.59 18.82	8.43 8.60)
$4b_2$	*p*-O_2N-C_6H_4	*p*-H_3CO-C_6H_4	180	42.08	$C_{31}H_{19}N_{10}S_2O_9$	45.38 (45.18	2.15 2.40	21.35 21.08	9.47 9.63)
$4c_1$	*m*-Cl-C_6H_4	*p*-Cl-C_6H_4	175	37.76	$C_{30}H_{17}N_9S_2Cl_2O_6$	49.34 (49.04	2.63 2.31	17.38 17.16	8.59 8.71)
$4c_2$	*m*-Cl-C_6H_4	*p*-H_3CO-C_6H_4	180	30.21	$C_{31}H_{19}N_9S_2ClO_7$	49.55 (49.39	2.34 2.69	17.67 17.88	9.36 9.08)



SCHEME-1

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